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INTERNAL MEDICINE

A Review of Fifty-One Cases of Multiple Myeloma
Harry Glenchur, Horace H. Zinneman, and Wendell H. Hall

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A Primer on Radiation Hazards for Physicians
Richard E. Peterson, Julius G. Baron, Bartis M. Kent, and Titus C. Evans

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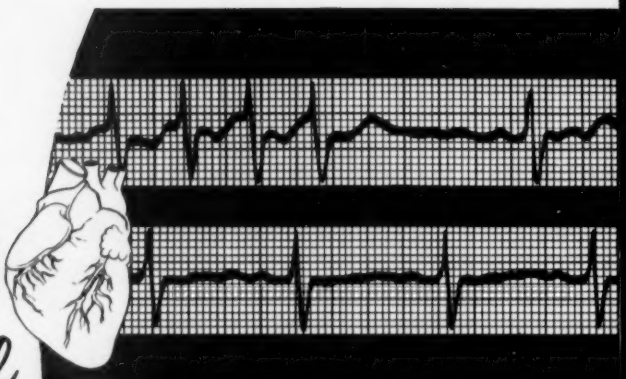

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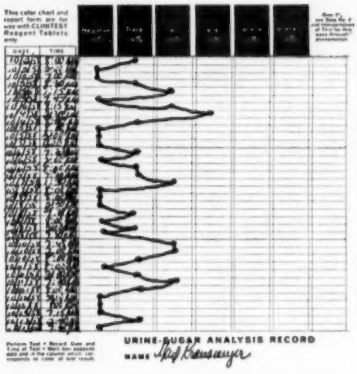

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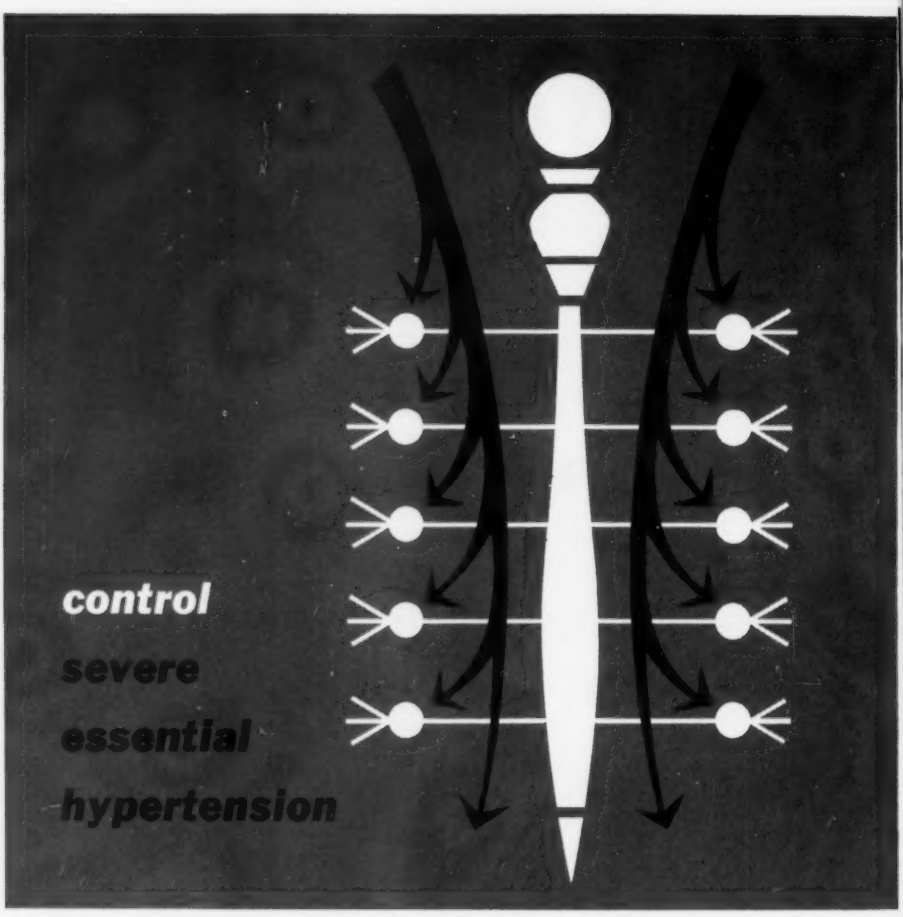

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**Revised 1958, Food and Nutrition Board, National Research Council, Washington, D.C.*

***Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1958.*
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

[1]*The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.*

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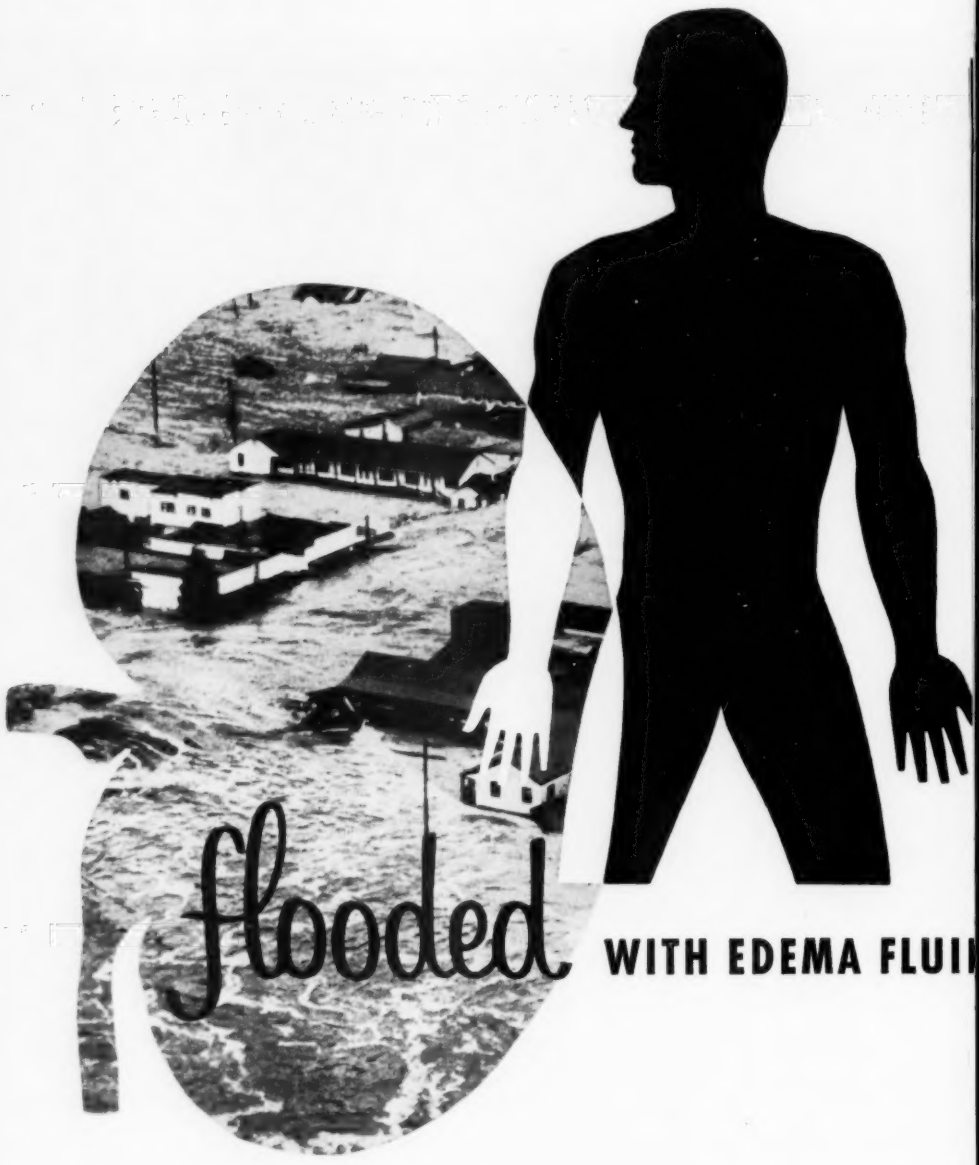

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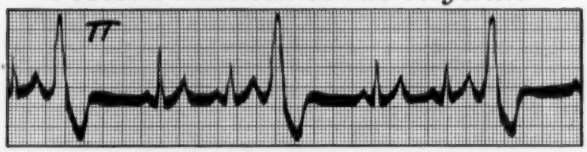

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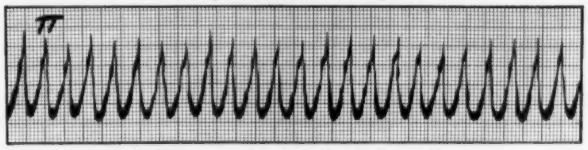
2. Paroxysmal auricular tachycardia



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References: 1. Burrell, Z. I., et al.: Am. J. Cardiol., 1:624 (May) 1958. 2. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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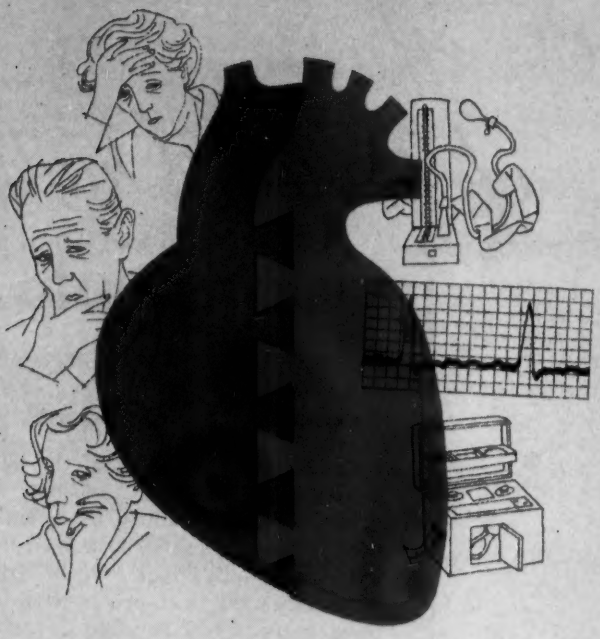

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INTERNAL MEDICINE

A Review of Fifty-One Cases of Multiple Myeloma

Emphasis on Pneumonia and Other Infections as Complications

HARRY GLENCHUR, M.D.; HORACE H. ZINNEMAN, M.D., and WENDELL H. HALL, M.D., Ph.D., Minneapolis

Since the discovery of numerous cases of recurrent bacterial infections resulting from agammaglobulinemia and lack of acquired serum antibodies in children and adults, there has been renewed interest in the general problem of resistance to infection. It has been shown recently that patients with multiple myeloma likewise are susceptible to recurrent bacterial infections, particularly pneumococcal pneumonia.[1-5] Zinneman and Hall [2] and Lawson and his associates [4] demonstrated that certain patients with multiple myeloma and large amounts of abnormal serum globulins had little or no normal γ-globulin or serum antibody. This fact seemed to account for their peculiar susceptibility to pneumococcal pneumonia.

Experiences at the Minneapolis Veterans Administration Hospital with 51 cases of multiple myeloma in the period from 1947 to 1957 are reported in the light of recent knowledge of protein abnormalities and with special emphasis on the incidence of infection, particularly bacterial pneumonia.

Materials and Methods

In each case, the diagnosis was established either by biopsy of bone marrow or accessible tumor or necropsy and serum-protein electrophoresis. Data which are of common knowledge and have been discussed in previous reviews will be mentioned only briefly.

Submitted for publication May 14, 1958.

From the Veterans Administration Hospital and the Department of Medicine, University of Minnesota.

Serum electrophoresis was performed either on paper or by the Tiselius method, with use of the portable model made by the American Instrument Company, operated at 10 ma. and allowing 120 minutes for separation. A barbital (Veronal) buffer was used at pH 8.6. The "ridgepole" method was used in paper electrophoresis, with use of Whatman No. 3 filter paper and a current of 6 ma. Ten hours were allowed for separation of proteins.

The 51 patients with multiple myeloma represent 0.05% of 101,956 admissions during the study period. Forty-two are dead, eight are living, and one has been lost to follow-up. Twenty-eight (55%) came to necropsy. Twenty-eight patients were followed by this hospital for an average of 3.4 admissions and two patient-year's care per patient. Fifteen patients died during their first admission, and eight patients were not seen after the first admission, being referred to private physicians, nursing homes, or other hospitals.

Eighty per cent of the patients were aged between 50 and 70 years at the time of first admission; the youngest was 26; the oldest, 73. The average age was 57 years. No difference in age incidence was noted in paraplegic patients or in those with pneumonia. The type and location of this hospital is reflected in the 100% maleness and Caucasian ancestry of the series.

Most patients presented themselves with one complaint. Thirty-four (67%) complained of bone pain, most frequently localized to the back and usually low in location. Six patients (12%) presented themselves with either pneumonia or a history of recurrent bouts of pneumonia over a period of several years. Three patients (6%) had primary complaints of pneumonia. Other initial complaints included weakness, anorexia, fatigability, tumor, paraplegia, and cough. Cough occurred to a troublesome degree in 35% of patients. It

was productive of white mucoid sputum and was not associated with pulmonary findings.

Other symptoms through the course of disease included pain (82%), weakness (69%), weight loss (53%), anorexia (45%), dyspnea (35%), bleeding phenomena (petechiae, epistaxis, bruising tendency, bleeding gums, subcutaneous hemorrhages) (31%), and constipation (28%).

Bone tenderness, the commonest physical finding, was found in 39 of 51 patients, mostly over the areas of pathological fractures or myelomatous involvement. Seventeen patients (33%) were found to have clinical hepatomegaly at some time during their course. Eight patients, believed to have hepatomegaly at necropsy, had no myelomatous involvement of that organ, but two had cirrhosis, and another, fatty infiltration of the liver. The liver of two additional patients was enlarged without pathological changes, and three patients had a normal-sized liver at necropsy. Only two patients were thought to have splenomegaly, which was borne out at necropsy. Nine patients (18%) had palpable tumors of either the skull, clavicle, sternum, rib, jaw, or pubis. Physical findings of pneumonia were present in 12 patients (24%). Pathological fractures were found in 32 patients (63%), most commonly in the ribs, vertebrae, and clavicles.

Twelve patients (24%) had hypertension. Their systolic blood pressure varied from 152-220 and the diastolic from 90-116 mm. of mercury. Five out of six hypertensive patients proved to have myelomatous kidneys at autopsy. Paraplegia was present in five patients (10%), with sensory changes up to the segments T5 to T12. Surgical decompression did not restore function. Herpes zoster or simplex was found in three patients. Other uncommon physical findings included pulmonary osteoarthropathy, shortened trunk due to vertebral collapse, and synovial thickening.

The only patient in this series demonstrating synovial thickening was a 62-year-old white man who had had "rheumatoid" arthritis for years, with exacerbation of joint pains one year prior to his admission for multiple myeloma. In addition to myeloma, he complained of aching and stiffness of his peripheral joints. Examination revealed limitation of motion of the painful joints, with striking synovial thickening of the elbows, wrists, fingers, and knees. The x-rays revealed demineralization of the bones of the joints, especially periarticularly; soft tissue swelling was minimal. Mild degenerative joint lipping was present in both elbows. Serum electrophoresis showed albumin, 3.2 gm. per 100 ml.; α_1-globulins, 0.2; α_2, 0.6; β- 1.1, and γ- 0.6 gm. per 100 ml. Urine electrophoresis disclosed a protein with the same mobility as β-globulin, which was considered identical to the Bence Jones proteins found in the urine. A Congo red test showed 24% dye absorption in one hour. The patient died in uremia. Postmortem examination revealed amyloidosis of the primary type, involving the parathyroid glands, and tumors of the ribs and right hip, pulmonary arteriolar walls, heart valves, and subendocardium. No myeloma cells were present in the rib and hip tumors, which may have been degenerated myelomatous tumors. No sections were taken of the joint capsules.

Since the completion of this survey, a second patient was admitted with marked synovial thickening. He was a 69-year-old white male barber who was well until five months before admission, when he noted weight loss and migratory joint pains. A physician found a profound anemia and proteinuria. Physical examination revealed a chronically ill white man with hepatomegaly. Synovial thickening, limitation of motion, and contractures of the wrists and the proximal interphalangeal joints were present. X-rays revealed generalized bony demineralization, periarticular swelling of the proximal interphalangeal joints, hypertrophic and compression deformities of the spine, and rarefactions in the skull. Biopsy of the bone marrow confirmed the diagnosis of multiple myeloma. Serum electrophoresis yielded the following fractions: albumin, 3.0 gm. per 100 ml.; α_1-globulins, 0.3; α_2-globulins, 0.9; β-globulins, 0.8, and γ-globulins, 1.5 gm. per 100 ml. There was Bence Jones proteinuria. Biopsy specimens of the alveolar ridge and synovium of the left wrist were positive for amyloid. Fluid from the left wrist joint showed predominantly neutrophils, with few lymphocytes (Figs. 1 and 2).

We found no convincing correlation between the hemoglobin level and the onset of roentgenographic findings typical of myeloma. Patients with solitary myelomas tended to have normal hemoglobin values, however. Multiple osteolytic lesions, pathological fractures, and demineralization of bones often coexisted with a normal hemoglobin level. Further, the early picture of myelomatous involvement of the skull, i. e., a granular appearance of the skull on x-ray, occasionally was associated with a moderate anemia. No patients with polycythemia were found. Seventy-two per cent of the patients had (admission) hemoglobin levels above 10 gm. per 100 ml. Profound anemia (less than 6 gm. per 100 ml.) was found in only two patients.

The average white blood cell count was 6,700 per cubic millimeter, with 64% neutrophils and 32% lymphocytes. The range varied from 11,000 to 1,600 per cubic millimeter. Twelve patients had leukopenia (less than 5,000 per cubic millimeter).

The initial erythrocyte sedimentation rate was within normal limits in 4 patients and between 10 and 50 mm. in one hour (Westergren) in 12

Fig. 1.—Deformity of wrists and proximal interphalangeal joints simulating rheumatoid arthritis in a patient with multiple myeloma. The deformities are due to periarticular deposits of paramyloid.

patients. During the hospital course it was noted that it fluctuated widely in 15 patients, with variance from above 100 mm. in one hour to normal. Three patients had macrocytosis; cirrhosis of the liver or hepatomegaly was found in all three at necropsy.

Plasma cells appeared in low numbers in the peripheral blood of 20 patients. Seven patients had histiocytes in the bone marrow. Rouleau formation was noted in 39 patients. Significantly, the total serum globulins of the patients with rouleau formation averaged 6.7 gm. %, while patients without rouleau formation averaged 3.1 gm. %.

The renal complications and urinary findings will be reported in detail elsewhere. Suffice it to say that 69% of the patients developed a heavy proteinuria (3+-4+) and had up to 50 white blood cells per high-power field in the urinary sediment. In the majority of the cases there was no associated urinary tract infection. Bence Jones proteinuria was found only in 14 cases. This is a much lower incidence than that commonly reported (50%) and may have been due to inadequate laboratory performance in earlier years. Presently, the urine is examined by the nitric acid-ring test and with sulfosalicylic acid as well as by paper electrophoresis. Urines with suggestive tests for Bence Jones protein are heated slowly in a water bath after adjustment to a pH of 5 and observed for turbidity developing with heat between 40 and 70 C. If the turbidity dissolves on continued heating to 100 C, Bence Jones protein is reported. Urines with persistent turbidity at the boiling point are filtered to remove albumin. Development of turbidity on cooling denotes presence of Bence Jones protein.

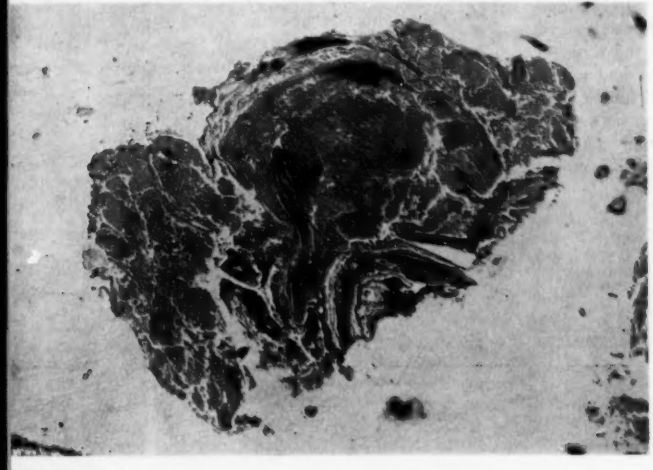

Fig. 2.—Photomicrograph (low magnification) of a biopsy specimen of synovium from a wrist joint, showing homogenous masses of amyloid deposited in subsynovial and periarterial locations.

TABLE 1.—*Results of Zinc Sulfate-Turbidity Tests in Relation to the Serum Globulins of Nine Patients with Multiple Myeloma*

Patient	Total Globulins, Gm/100 Ml	Globulin Fractions, Gm/100 Ml					Zinc Sulfate Turbidity
		α_1	α_2	β	γ	"M"	
1	3.1	0.4	0.9	1.1	2.5		30.7
2	4.5						11.5
3	5.7	0.2	0.3	0.5	3.5		30
4	6.0	0.1	0.3	0.3	0.3	4.7	50
5	6.2						68
6	8.3		0.6	0.5	6.6		47.8
7	9.0		0.8	1.3	7.0		34.3
8	12.9						72
9	14.0						121

Fifteen cases of kidney myeloma were found at necropsy. Three other patients died in renal insufficiency but did not come to autopsy.

Serum-cholesterol determinations were carried out for 11 patients. Low values, averaging 149 mg. %, were found in all these patients and probably reflect their poor nutritional status. Liver-function studies were done for 29 patients and included all or part of the following tests: sulfobromophthalein (Bromsulphalein) retention, serum bilirubin, thymol turbidity, zinc sulfate turbidity, and cephalin-cholesterol flocculation. All serum-bilirubin determinations were within normal limits. The sulfobromophthalein retention, thymol turbidity, and cephalin-cholesterol flocculation tests were abnormal only in the few cases whose livers were cirrhotic or fatty. This is somewhat at a variance with the experience of Snapper, Turner, and Moscovitz, who found elevated cephalin-cholesterol flocculation levels in 19% of their series.[1]

The zinc sulfate-turbidity tests were elevated in nine patients, to a maximum of 121 units (Table 1). Of these, there were four patients with a γ-type myeloma, one "M" type myeloma with hepatic cirrhosis, and four patients from whom an electrophoretic fractionation of the serum protein had not been obtained but who had a pathologic increase of their total serum globulins. There appeared to be a rough correlation between the zinc sulfate turbidity and the globulin content of the serum. All of four patients with normal zinc sulfate turbidity had low serum globulins except one, who had an elevated serum β-globulin.

Electrophoretic patterns of the serum proteins were obtained for 31 patients: 15 (48%) were of the γ-type; 6 (19%) revealed low γ-globulins; 5 (16%) were of the β-type; 3 were of the "M"-type, and 2 revealed normal patterns (Table 2). Cryoglobulinemia was not found on testing seven patients' sera; one patient's serum was reported to gel at low temperatures, but a check for precipitable cryoglobulins was not done. Pyroglobulinemia was proved in one case; solidification of the serum occurred at 55 C. Ultracentrifugation for macroglobulins was not done.

Three patients with γ-type myelomas and three patients with low serum γ-globulins had repeated electrophoretic studies of their sera. Two of the three γ-type patients exhibited a progressive increase of the γ-globulins. Two of the three patients with low γ-globulins showed a gradual decrease of γ-globulins with progression of their myeloma. The pattern remained the same, however.

A correlation of the patients' survival time (from onset of symptoms to death) with the type of serum electrophoretic pattern is shown in Table 3. Those patients, typed as having β-myeloma, had a shorter average duration of life.

The results of therapy were not impressive except perhaps for the amelioration of pain after deep roentgen radiation. The want of a satisfactory

TABLE 2.—*Serum-Electrophoretic Patterns in Thirty-One Patients with Multiple Myeloma*

Electrophoretic Pattern	Patients, No.	%
γ	15	48.5
β	5	16
"M"	3	10
Low γ-globulin	6	19
Normal	2	6.5

TABLE 3.—*Correlation of Average Survival Time of Twenty Myelomatous Patients with the Characteristics of Their Abnormal Serum Globulin*

Myeloma Type (Serum Electrophoresis)	Patients, No.	Duration of Course, Mo.	
		Average	Range
γ	6	25.3	9-60
Low globulin	6	26.6	3½-60
"M" myeloma peak	3	23.7	6-38
β	4	14.0	7-25
Normal	1	10	—

TABLE 4.—*Bacteriologic Findings and Serum Protein Patterns in Twenty-Eight Patients with Multiple Myeloma and Pneumonia* *

Patient	Date	Location	Bacteriology		Myeloma Type	Remarks
			Sputum	Blood		
1	1954	NH			γ	
	Spring '55	NH				
	11-14-56	RLL, LUL	Kleb.			
2	5-1-50	LLL, NH			γ	
	11-1-50	RLL	D. pn. VI			
	1-8-51	RLL	D. pn. VI			
3	3-3-55	LLL			γ	
4	8 early bouts					
	1-12-55	RLL	D. pn. XX	D. pn. XX	γ	
	2-10-56	RUL, LLL				
5	7 early bouts					
	3-4-55	LLL			γ	
	12-13-55	RUL, RML, LUL				
	9-14-56	LLL				
	12-18-56	LLL				
	1-5-57	RLL				
6	3-49	NH			γ	
	2-50	NH				
	3-50	NH				
	4-1-50	Left lung	D. pn. V			
7	12-4-56	RLL			γ	
8	12-13-56	RLL	D. pn. VII	D. pn. VII	γ	Herpes simplex
9	Fall '55	NH			Decr. γ	
	8-20-52	? loc.			Globulins	Leukopenia
10	5-18-53	RLL			Decr. γ	
11	10-30-56	RLL			Decr. γ	
	10-8-57	RLL, LLL			Decr. γ	
12	4-4-56	RLL			Decr. γ	
	8-2-56	RML, RLL, LLL			Decr. γ	
13	3-18-51	RML			Decr. γ	
14	4-28-50	LLL			Decr. γ	
15	5-25-44	RLL			Unknown, high globulin	
16	11-47	NH			Unknown, high globulin	
	3-48	NH				
	1-49	NH				
	2-49	NH				
	3-49	NH				
	6-49	LLL				
	2-28-50	RUL, RLL	D. pn. III			Hgb. 3.6 gm. %
17	3-6-50	LLL			Unknown, high globulin	Pleural effusion, slow resolution, cyanosis
	12-24-50	RLL, LLL	D. pn. XIX			
	1-16-52	NH				
18	6-6-47	LLL			Unknown, high globulin	
	6-1-48	RLL				
	6-28-48	RLL				
19	4-25-47	RUL, LUL			Unknown, high globulin	
20	7-2-46	RLL			Unknown, high globulin	
21	Spring '47	NH			Unknown, high globulin	
	Fall '47	NH				
	Fall '47	NH				

22	4-10-47	LLL	Unknown, high globulin	
23	12-18-53	RLL	Unknown, high globulin	
24	10-21-53	LLL	Normal	
25	5-6 bouts	NH	"M" peak	
26	10-1-53	LUL, LLL	"M" peak	Slow resolution, cyanosis
27	11-26-56	LLL, RLL	β	Hypotension
28	12-11-56 1-9-57	LUL RLL	β	

* NH indicates not hospitalized; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; LUL, left upper lobe; D. pn., Diplococcus pneumoniae, type; Kleb., Klebsiella; Prot., Proteus; Staph., Staphylococcus pyogenes; N. cat., Neisseria catarrhalis.

therapeutic regimen is reflected in the multiplicity of drugs administered, including urethan, stilbamidine, adrenocortical steroids, radioactive phosphorus, and mechlorethamine hydrochloride (nitrogen mustard). The most frequent therapeutic regimen administered was urethan and x-ray or x-ray alone (12 and 9 patients, respectively). Twenty patients received urethan alone or in combination with other therapy (x-ray, adrenosteroids, corticotropin [ACTH]). Five patients received adrenal steroids or corticotropin alone. Eight patients received no therapy. Stilbamidine was used in three patients. Ten patients received corticotropin or adrenal corticosteroids alone or in combination with other therapy. Their average duration of life was 10 months, ranging from 6 days to 26 months. The average duration of life for all other patients was 27.5 months, with a range of 7-74 months. The evaluation of therapy is inconclusive since the number of patients treated under each of the various regimens was small in number.

The average duration of the disease in 39 patients with known onset of symptoms was 23 months. The longest course was six years two months; the shortest, three and one-fourth months. Serum proteins of the patient who survived for six years two months contained 2.1 gm. of albumin per 100 ml. and 7.0 gm. of globulins per 100 ml.; electrophoretic fractionation was not available at the time.

Results

As reported in 1954, patients with multiple myeloma have been noted to have a marked tendency toward recurrent bouts of bacterial pneumonias.[2] We have been impressed with the high incidence of pneumonia, both recurrent and terminal, in the present series of patients. For this reason we wish to emphasize this aspect as a serious complication of multiple myeloma.

Twenty-eight patients (55%) experienced one or more episodes of pneumonia, exclusive of terminal pneumonias, during the course of their disease (Table 4). A total of 76 episodes of pneumonia was experienced by these patients, averaging 2.7 bouts per patient. The bacteriologic findings are indicated only when the bacteria isolated were frank pathogens. The diagnosis of pneumonia was obtained by history, physical examination, chest x-ray, and isolation of the bacterial pathogen from the sputum or blood. The results of therapy were good, except in two patients who experienced slow resolution.

In two patients prophylaxis with either sulfadiazine or penicillin orally did not appear to prevent further attacks of pulmonary infection, but the patients were not conscientious about their medications.

The majority of infections involved the lower lobes, more frequently the right lower lobe. Pathogenic bacteria were isolated in only eight episodes of pneumonia. Normal inhabitants of the oral-respiratory tract (Neisseria, diphtheroids, viridans Streptococcus and Candida species) were isolated in other cases.

Electrophoresis of the serum of these 28 patients with pneumonia revealed a γ-myeloma pattern in 8. Protein determinations on nine patients' serum revealed high globulin content (greater than 4 gm. per 100 ml.), but the pattern type is unknown. Seven patients' serum had no globulin elevation on

TABLE 5.—*Terminal Pneumonia in Seventeen Patients with Multiple Myeloma*

Patient	Location *	Bacteriology *		Therapy †	Myeloma Type	Remarks
		Sputum	Blood			
1	LLL				γ	Died ruptured aneurysm
2	RML, RLL, LLL	Prot.		C, P	γ	
3	RLL			P	γ	Cyanosis, developed while on penicillin
4	RUL (Abscess) LLL			P	Low γ-globulin	
5	RLL, LLL	Staph.			Low γ-globulin	
6	RLL, LLL			P	Low γ-globulin	Hypotension, semiconscious develop. while on penicillin
7	LUL, LLL			P	"M" peak	Shock
8	LUL, RUL, LLL				β	Pyroglobulinemia
9	RUL, LUL			P, SM	Unknown, low globulin	
10	RLL				Unknown, low globulin	Cyanosis
11	RUL, RLL	D. pn. III		P	Unknown, high globulin	Nonresponsive
12	RLL, RML			P	Unknown, high globulin	
13	LUL, RLL		Prot.	P, SM	Unknown, high globulin	Cyanosis, hypotension
14	RLL, LLL			P	Unknown, high globulin	Cyanosis
15	Scat. foci			P	Unknown, high globulin	
16	RLL, LLL				Unknown, high globulin	Discovered by necropsy
17	RML, RLL	D. pn. XIII	D. pn. XIII	P, CTC	Unknown, high globulin	Pneumonia spread while on therapy

* For explanation of abbreviations, see Table 4.
† P indicates penicillin; C, chloramphenicol; SM, streptomycin.

electrophoresis; in six the γ-globulins were low. Two had a β-myeloma pattern, and the serum of two others exhibited an abnormal "M"-myeloma peak. Only one patient with pneumonia had a normal serum protein pattern. It is readily apparent that recurrent pneumonia may occur with all types of myeloma patterns. The preponderant number of γ-patterns in this series of recurrent infections is representative of the greater incidence of γ-type myelomas (Table 2). In these γ-myelomas and some of the β- and "M"-type myelomas, the normal γ-globulin is diminished or absent. The serum-protein abnormality in several others consisted of an significant decrease of γ-globulins (less than 1.0 gm. per 100 ml.). The common denominator of the protein patterns in patients with myeloma and recurrent pneumonia is a *decrease* of normal (immunologically active) γ-globulin.

Table 5 is a tabulation of the terminal pneumonias demonstrated either just prior to death or at necropsy. Seventeen of the fifty-one patients (33%) in this series died with pneumonia. It is significant that in the majority of these cases antibiotic therapy, though previously effective, did not prevent a rapid terminal course. Bacteremia occurred in two patients. In addition, cyanosis, hypotension, and peripheral vascular collapse were common.

The leukocyte response to pneumonia was significantly lower than normal. The average white cell count at the time of infection was 8,860 per cubic millimeter, with 75% neutrophils.

The frequency of infection is further emphasized by the necropsy findings. Nineteen of twenty-eight autopsies revealed pleural adhesions (68%) indicative of previous pulmonary infections. Roentgenography had indicated pleural thickening in only 11 of 51 cases.

As seen in Table 6, bacteremia was demonstrated in 7 of the 51 cases (14%). It may be significant that the three patients who survived a bacteremia had an adequate leukocytic response with neutrocytosis. In one patient there were two episodes of bacteremia, the second caused by Neisseria catarrhalis, which is ordinarily not invasive.

Twenty-nine patients (57%) experienced other infections, exclusive of pneumonia and bacteremia. This might be the result, in part, of age and debility. Five patients were

TABLE 6.—*Myelomatous Patients with Bacteremia*

Patient	Blood Culture *	Primary Focus	Therapy †	Result	WBC	PMN	Myeloma Type
1	H. staph. (C+)	Ischiorectal abscess	E, CTC	Died	1,800	35	β
2	Proteus	Decubitus ulcer	P, S	Died	8,900	72	Unknown, high globulin
3	D. pn. VII	Bronchopneumonia	P, C	Good	10,000	91	γ
4	D. pn. XIII	Bronchopneumonia	P, CTC	Died	6,700	80	Unknown, high globulin
5	E. coli	Unknown	P	Died	3,200	51	Unknown, high globulin
6	D. pn. IX	Probably URI	P, S, C,	Good	12,700	92	γ
7	D. pn. XX N. cat.	Bronchopneumonia, pharynx?	S, P	Good	11,950	81	γ

* For explanation of abbreviations, see Table 4.

† E indicates erythromycin; P, penicillin; CTC, chlortetracycline (Aureomycin); S, streptomycin; C, chloramphenicol (Chloromycetin).

found to have herpes or coryza; there were no other viral infections. Only one patient demonstrated a chest x-ray suggestive of active pulmonary tuberculosis. Table 7 lists

TABLE 7.—*Infections Other than Pneumonia Encountered in Fifty-One Patients with Multiple Myeloma*

Infection	Patients, No.
Urinary tract infections	17
Thrombophlebitis	3
Meningitis, purulent	3 (2 found at necropsy)
Decubitus ulcers	3
Herpes zoster or simplex	4
Otitis media	2
Otitis externa	2
Prostatitis	2
Cellulitis, localized	2
Ischiorectal abscess	1
Endophthalmitis	1
Epiglottic abscess	1
Furuncles	1
Coryza	1
Fungus skin infection	1
Chronic Cholecystitis	1 (found at necropsy)

the various infections occurring throughout the course of these patients' disease. Urinary tract infections predominated and could be ascribed to prostatic hypertrophy or neurogenic bladder dysfunction requiring prolonged indwelling bladder catheters. Renal lithiasis was present in two patients. An unsuspected finding was the presence of purulent basilar meningitis at the necropsy of two patients. Unfortunately, no cultures were obtained. A third patient was admitted with acute pneumococcal meningitis.

Comment

In this series of 51 patients, 28 (55%) had a history of at least one episode of pneumonia, exclusive of terminal pneumonias. One patient had 12 bouts of pneumonia over a period of several years. The average number of pneumonic episodes for these 28 patients was 2.7 after the onset of the myeloma.

Geschickter and Copeland mentioned the frequency of chronic bronchitis and emphysema in patients with multiple myeloma.[3] They believed the following factors are responsible for chronic bronchitis and emphysema in myelomatous patients: (1) debilitated states, (2) hypostatic changes dependent on long periods of bed rest, and (3) restricted alveolar ventilation brought about by painful respiration.

It was not until 1953 that the problem of recurrent pneumonia was first mentioned by Snapper, Turner, and Moscovitz. Twenty-four patients in their series of ninety-seven had at least one episode of pneumonia, exclusive of terminal pneumonia. Thirteen patients had recurrent pneumonia, and several of these had five or six episodes within a two-year period. Snapper, Turner, and Moscovitz believed that recurrent pneumonia occurred most frequently in patients with highly elevated serum globulins and that the recurrent bouts of pneumonia were secondary to repeated small pulmonary infarcts.[1] They listed as additional factors (1) kyphosis of the dorsal spine with resultant pulmonary emphysema, (2) sluggish pulmonary circulation related to the high serum globu-

lin, with increased blood viscosity and tendency to rouleau formation of the red blood cells, and (3) often markedly decreased antibody levels in the serum of myeloma patients. Snapper, Turner, and Moscovitz believed these combined factors were a perfect medium for the formation of small pulmonary infarcts, which then became secondarily infected and simulated the picture of recurrent bronchopneumonic episodes.[1]

In our experience recurrent pulmonary infections usually have occurred in patients who are up and about, albeit with moderate restriction of activities. This fact would tend to rule out the influence of debilitation, restricted alveolar ventilation, and pulmonary hypostatic changes which may be contributory to the development of pneumonia in the terminal phase of the disease.

In addition, our patients with recurrent pneumonia did not have any consistent degree of kyphosis or pulmonary emphysema. It is possible that the hyperglobulinemia and concomitant increase in blood viscosity delay and impede pulmonary circulation, but this is an unproved conjecture. Chronic cor pulmonale is not frequent in these cases.

In our 28 cases which came to necropsy, only 1 exhibited histological evidence of multiple small pulmonary infarcts, such as hyaline thrombi in the smaller blood vessels.

Zinneman and Hall showed, in 1954, that these patients have a poor antibody response to antigenic stimuli.[2] They subjected 10 myelomatous patients, who did not have pneumonia at the time, to challenges with the polysaccharides of the Diplococcus pneumoniae (pneumococcus) and Brucella and with typhoid-paratyphoid vaccine. Antibody production occurred in inverse proportion to the total amount of abnormal serum globulins. No antibodies were demonstrable in sera which contained large amounts of abnormal globulins, whereas an antibody response was elicited in the serum of patients with normal or near-normal electrophoretic patterns. It was suggested that the immunologic response of patients with multiple myeloma was comparable to that of patients with agammaglobulinemia, the common denominator being a profound reduction of the immunologically active serum globulins.

Lawson and his associates independently reported similar findings.[4] They studied agglutinin formation in myelomatous patients to Salmonella typhosa, Paracolobactrum ballerup, Escherichia coli, and sheep erythrocytes; type-specific agglutinins for human A and B erythrocytes; lysins for S. typhosa, E. coli, and sheep cells. The titer of complement activity was normal in all cases. In nine myelomatous patients, four showed no antibodies, including blood-group antibodies. In the other five, some antibodies were present in the serum, but only one case had what was considered a normal content of these substances. Repeated testing showed a decrease in number and titer of antibodies and, in two patients, complete disappearance over a period of a year. Electrophoresis of the serum of five patients showed four γ- and one "M"-type of myeloma protein pattern.

Porges, using a modified filter-paper-electrophoresis technique, also tended to support this thesis. Two myeloma patients with recurrent pneumonias had no normal γ-globulin, whereas a third myeloma patient without recurrent infection possessed normal γ-globulin.[5]

Neutropenia or agranulocytosis may be another factor leading to infections. Vaughn and Raphael reported a myelomatous patient with a white cell count of only 1,000 per cubic millimeter and no neutrophils in the peripheral blood who succumbed to a staphylococcal infection of the lungs.[6] No instance of agranulocytosis was found in our 51 cases.

The factors contributory to the recurrence of pneumonias in multiple myeloma are probably multiple and additive. It would seem that defective antibody production is the most important factor in the increased susceptibility to infection, especially in those cases with large amounts of globulin in the serum. This situation is akin to agammaglobulinemia, in which there are recurrent episodes of respiratory infections, pneumonia, bronchiectasis, and pneumococcal meningitis over a period of several

years.[7] Although the serum γ-globulins in multiple myeloma and agammaglobulinemia are diametric opposites by quantitative measurement, with an abnormal excess in one and near absence in the other, they have in common a profound reduction of the immunologically active serum globulins.[2]

Seventeen patients died with pneumonia, either as a direct cause or as a concomitant finding. This is in agreement with other series and reflects both the increased susceptibility of myelomatous patients to infection, the debilitated state, and the inexorable course of the disease.

Seven cases of bacteremia in this series show that the inability to produce effective antibodies leads to serious infections other than pneumococcal respiratory infections. Bacteria isolated from the blood included the Staphylococcus, Proteus, E. coli, and Neisseria catarrhalis. The incidence of bacteremias (14%) appears to be higher than chance would permit.

Three of seven patients tested for tuberculin sensitivity had positive skin reactions. This delayed type of bacterial hypersensitivity often is interpreted as a sign of increased host resistance against the bacterial antigen. For clinical purposes, this delayed hypersensitivity often parallels bacterial resistance, although it has been demonstrated conclusively that it is not necessarily associated with an increase of resistance to infection with tubercle bacilli.[8]

Good and Varco believed that patients with agammaglobulinemia had difficulty developing delayed bacterial hypersensitivity.[9] Subsequently, however, several patients have been reported with a positive tuberculin skin test in the presence of agammaglobulinemia.[10-15]

Passive transfer of tuberculin sensitivity cannot be accomplished with the whole serum of a tuberculin-positive animal, but the transfer of a wide variety of its living or killed mesenchymal cells will cause local tuberculin sensitivity in a normal animal.[16]

One case in the series of fifty-one cases had arthritis resembling rheumatoid arthritis, and subsequently another similar case was admitted. Both patients demonstrated widespread amyloid disease of the primary type. Unfortunately, only the latter case had a synovial biopsy, which demonstrated amyloid. Such cases of "rheumatoid arthritis" in multiple myeloma are not unknown. Arthritic symptoms may precede the diagnosis of multiple myeloma. Eight cases previously reported all had amyloidosis complicating their myeloma.[17] An arthritic-like syndrome has been reported in cases of congenital or acquired agammaglobulinemia; amyloid disease has not been implicated in these cases.[18] The mechanism by which "amyloid" is formed in cases of myeloma is as poorly understood as is the source of "fibrinoid" in rheumatoid arthritis and other collagen diseases. Since they have been observed in patients with diminished normal γ-globulin and serum antibody, it seems unlikely that in these cases these tissue changes are the result of an antigen-antibody reaction as is commonly thought. The role of tissue allergy of the delayed (bacterial) type has not been excluded.

Summary

Fifty-one consecutive cases of multiple myeloma are reviewed. The onset, age incidence, clinical findings, and course were in essential agreement with the previously reported series. There were 18 cases with myelomatous kidneys. Ten per cent of the patients presented themselves with the findings of paraplegia. Two cases with "rheumatoid arthritis" had amyloidosis complicating myeloma.

Fifty-five per cent of 51 patients experienced one or more episodes of pneumonia, exclusive of terminal pneumonia, averaging 2.7 bouts per patient. Only one of these patients had a normal serum protein electrophoresis pattern. Terminal pneumonia occurred in 17 of the 51 patients. Seven of the fifty-one patients experienced bacteremia. In addition, 57% of patients had other infections, predominantly of the urinary tract.

The high incidence of recurrent pneumonia is impressive. This is a consequence of the inability to produce protective antibodies, as in agammaglobulinemia. As in agammaglobulinemia, the delayed type of bacterial hypersensitivity is not altered in multiple myeloma.

Repeated bacterial infections, especially pneumococcal pneumonia, should be emphasized as an important and often early complication of multiple myeloma. Antibiotics are effective unless their use is delayed.

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The Treatment of Moderate and Severe Pneumococcal Pneumonia with Oral Phenoxymethyl Penicillin

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The successful treatment of pneumococcal pneumonia with oral phenoxymethyl penicillin (penicillin V) has been reported by several investigators.[1-3] Because encouraging results of therapy observed during a single season are often not confirmed by study over a longer period of time it is always reassuring to report the repetition of therapeutic trials which at first show promise. The present report, therefore, adds our experience of 1956-1957 to that of 1955-1956, which was the basis of our first communication on this subject.[1] The second year, in general, confirmed the initial experience.

Plan of Study

The plan of study was similar to that of the first year of the program. All patients with pneumonia admitted to the Cincinnati General Hospital were screened by one of us and included in the study with the following exceptions: (1) those suspected of having nonpneumococcal pneumonia; (2) those unable to take oral medication, usually because of coma, shock, or ileus; (3) those receiving prior or additional antibiotic therapy; (4) one patient with known penicillin sensitivity, and (5) those with malignant lung disease, congestive heart failure, or tuberculosis so severe as to make evaluation of the pneumonia difficult. These three conditions, when not severe, did not preclude the use of phenoxymethyl penicillin. Two patients who died within six hours are not included in the series.

As in the previous year, the criteria for the diagnosis of pneumonia included a history of pneumonia, physical findings of consolidation, roentgenographic evidence of pulmonary infiltrate, the demonstration of Gram-positive diplococci on the smear of the fresh sputum, and a clinical course compatible with the disease.

Pretreatment sputum and blood cultures were obtained from all patients. Sterile cotton-tipped applicators dipped in the fresh sputum were incubated overnight in brain-heart-infusion broth. Any pneumococci present were typed with specific rabbit antisera, with use of the quellung reaction. Though the routine use of mouse inoculation always increases the proportion of pneumococci recovered from the respiratory tracts of patients with pneumococcal pneumonia, the use of this procedure is not feasible in our laboratory. Patients whose initial smear showed lancet-shaped Gram-positive diplococci but from whom pneumococci were not recovered by culture were included in this series only after careful evaluation.

Those patients who were not admitted to the study are presented as a separate group in order to show the reasons for their exclusion, the severity of their illness, and their response to antibiotic therapy. In addition to patients excluded for these stipulated reasons, nine more were excluded because they were given one or more doses of penicillin G intramuscularly by new rotating interns who failed to comprehend the purpose of the study!

In contrast to the previous year's investigation, when several dosage schedules were explored, all patients in the present report were treated with oral phenoxymethyl penicillin, 250 mg. on admission and every six hours thereafter for the duration of therapy. This series, like that of the previous year, contains primarily moderately and severely ill patients. Owing to frequent scarcity of hospital beds, those patients with small infiltrates and mild toxicity were treated as outpatients, with parenteral penicillin.

Results

Etiology.—Sixty-eight patients were studied in 1956-1957. Gram-positive diplococci were found in significant numbers on the

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TABLE 1.—*Pneumococcal Types Recovered from Patients with Pneumonia, 1955-1957*

Type	Patients Included in Phenoxymethyl Penicillin Program			Patients Excluded from Phenoxymethyl Penicillin Program
	1955-1956	1956-1957	Total 1955-1956-1957	1956-1957
1	6	7	13	3
2	1	3	4	1
3	3	3	6	4
4	6	4	10	--
6	--	3	3	4
7	5	3	8	2
8	5	2	7	3
12	--	4	4	1
Misc.*	3	10	13	14
	29	39	68	32

* Type 14, 4; Type 17, 3; Type 23, 4: Pool A (Types 1, 2, and 7), Pool B (Types 3, 4, 5, 6, and 8), and untyped (bile soluble), 2 each. One each of Types 11, 13, 21, 22, 25, 31, 34, Pool C (Types 9, 12, 14, 15, 17, and 33), and Pool D (Types 10, 11, 13, 20, 22, 24, and 34).

smear of the admission sputum in each case. In 39 (57%) of the 1956-1957 patients pneumococci were typed or identified by bile solubility. This percentage is less than the percentage of typeable pneumococci recovered in 1955-1956, namely, 70%. The type distribution is given in Table 1.

Severity.—Three patients (4%) in the 1956-1957 series and 6 (14%) in the 1955-1956 series had bacteremia. We are at a loss to explain the low bacteremic rate in this series of seriously ill untreated patients. Fifty patients (73%) in 1956-1957 had one lobe involved; 17 (25%) had two lobes involved, and 1 had three lobes of pneumonia. Forty-three patients (63%) were considered moderately ill, 23 (37%) severely ill, and 2 (3%) critically ill. Ages ranged from 14 to 80 years.

The white blood cell count on admission varied from 4,000 to 85,000 per cubic millimeter. While only one patient had a white blood cell count below 5,000, twenty-six (38%) had counts greater than 20,000 per cubic millimeter. Thirty-three patients (49%) had one or more of the following concomitant or complicating diseases: chronic alcoholism, 21; chronic lung disease, 9; uncontrolled diabetes, 2; heart failure, 4; chronic renal disease, 3; anemia, 2; cerebral vascular accident, 1, and toxic jaundice, 1. This distribution of concomitant diseases is similar to that reported in 1955-1956.

Results of Treatment.—Fifty-nine patients (87%) in 1956-1957 responded within 24 hours to oral phenoxymethyl penicillin with marked clinical improvement and prompt lysis of fever. The average duration of fever was 1.8 days, and no patients remained febrile beyond the 4th day. If we exclude two patients whose treatment was inadvertently continued longer than necessary, the duration of therapy ranged from 3 to 14 days, with an average of 9 days. Although none of these patients were regarded as "critically" ill, 17 were severely ill, and 26 had one or more of the concomitant or complicating diseases mentioned. For the two years, the percentage of "excellent" responses was 84.

Satisfactory but Submaximal Response.—Six patients (9%) in the 1956-1957 study responded with slow resolution of the pneumonia or the occurrence of a prolonged febrile period. None of these patients was critically ill, but one had bacteremia, and four others had severe complicating diseases. These six cases will be described separately.

CASE 1.—A severely ill 53-year-old man was admitted with right lower lobe pneumonia. Type 2 pneumococcus (Diplococcus pneumonia) was cultured from his blood and sputum. He was treated with phenoxymethyl penicillin, 250 mg. every 6 hours for 14 days. Although he was clinically improved after 24 hours, his fever continued for seven days, and his pulmonary infiltrate cleared slowly over a five-week period.

CASE 2.—A severely ill 31-year-old alcoholic was admitted with right upper lobe pneumonia and marked dehydration. Her blood was sterile, but a Type 19 pneumococcus was cultured from her sputum. Although she improved rapidly on the phenoxymethyl penicillin regimen, she developed fever and an effusion in the right middle lobe fissure on the 11th day. Phenoxymethyl penicillin was continued for 16 days. She was discharged afebrile on the 23d day, and the roentgenogram of her chest was clear in two months.

CASE 3.—A severely ill 48-year-old uncontrolled diabetic was admitted with bilateral lower lobe pneumonia. Although Gram-positive diplococci were

found on a smear of the fresh sputum, no pneumococci were cultured from the blood or sputum. He was given phenoxymethyl penicillin, 250 mg. every six hours for 11 days, with lysis of fever in 5 days and slow resolution of the infiltrate over a 2-month period.

CASE 4.—A severely ill 38-year-old alcoholic, who years before had had a right upper lobectomy and right "phrenic crush" for tuberculosis, was admitted with consolidation of the left upper lobe. Gram-positive diplococci were found on a smear of the fresh sputum but not in culture of the blood or sputum. He was given 250 mg. of phenoxymethyl penicillin every six hours for seven days. Except for delirium tremens and slow resolution of fever over a six-day period, his recovery was uneventful.

CASE 5.—A severely ill 53-year-old man was admitted with consolidation of his right upper lobe. Gram-positive diplococci were found on the smear of his sputum but not in blood or sputum culture. He received 250 mg. of phenoxymethyl penicillin every six hours for 11 days with prompt clinical improvement, but his fever remitted slowly over a 5-day period.

CASE 6.—A 67-year-old woman with bronchial asthma and emphysema was admitted severely ill with pneumonia of the right middle and lower lobes. Fresh smear of the sputum showed Gram-positive diplococci, but none were found on culture of the blood and sputum. She received phenoxymethyl penicillin, 250 mg. every six hours for nine days, with lysis of her fever in five days and resolution of her pulmonary infiltrate over a five-week period.

Unsatisfactory Results.—The response of three patients (4%) in 1956-1957 was unsatisfactory. Two died, and the third developed the purulent complications of pericarditis and empyema but recovered after a prolonged hospital stay. These patients will be described in detail.

CASE 7.—A demented, critically ill 69-year-old white woman with uncontrolled diabetes, marked dehydration, pulmonary emphysema, and bilateral lower lobe pneumonia was admitted to the hospital from a nursing home. The culture of the sputum yielded a Type 6 pneumococcus, but the blood was sterile. Her temperature was 102 F; white blood cell count, 29,000 per cubic millimeter; fasting blood sugar, 492 mg. %; blood urea nitrogen, 55 mg. %, and CO_2-combining power, 37.5 mEq. per liter. She was given phenoxymethyl penicillin, 250 mg. every 6 hours, but was unimproved after 20 hours. Gastric dilation and progressive hypotension developed. Despite treatment with norepinephrine (arterenol) she died in shock 23 hours after admission. Autopsy revealed an extension pneumonia involving the right middle and lower lobes and the left lower lobe.

CASE 8.—A 74-year-old Negro woman with hypertension and chronic uremia secondary to chronic pyelonephritis was admitted severely ill with right lower lobe pneumonia. Gram-positive diplococci were seen on smear of fresh sputum, but pneumococci were not cultured from sputum or blood. Her hemoglobin was 7.5 gm. %; white blood cell count, 11,000 per cubic millimeter, and blood urea nitrogen, 76 mg. %. The urine showed a 4+ reaction for albumin. For five days she was given phenoxymethyl penicillin, 250 mg. every six hours, without improvement. Because of a falling blood pressure on the fifth day, her therapy was changed to intramuscular procaine penicillin G, 600,000 units every 12 hours. Cheyne-Stokes respiration, pulmonary edema, acidosis, oliguria, and hypotension ensued, and she died on the ninth hospital day. Autopsy revealed an extensive pneumonia of the entire right lung. Gram-stained sections of the lung showed numerous Gram-positive diplococci. Also present were severe chronic pyelonephritis, myocardial hypertrophy, and far-advanced coronary arteriosclerosis.

CASE 9.—A 34-year-old critically ill alcoholic was admitted to the hospital, delirious, faintly jaundiced, and with consolidation of the right middle and lower lobes. Type 7 Pneumococcus was cultured from sputum and blood. Temperature was 104 F; pulse, 120; respiratory rate, 42 per minute; white blood cell count, 7,400 per cubic millimeter, and serum bilirubin, 2.3 mg. %. During the five days he was given phenoxymethyl penicillin; clinical toxicity markedly dimished, but temperature as high as 102 F persisted. When a pericardial friction rub was discovered on the fifth day, therapy was changed to intramuscular penicillin G, 1,000,000 units every six hours. The ninth day, the white blood cell count rose to 30,000 per cubic millimeter and fever persisted. Because both physical examination and x-ray demonstrated an enlarging cardiac silhouette, pericardial aspiration was performed. It yielded 130 cc. of serosanguinous fluid containing 750 white blood cells and 22,000 red blood cells per cubic millimeter. The specific gravity was 1.025, and the protein, 3.8 gm. %. No bacteria were found in culture or smear. This pericardial fluid, aspirated one hour after an intramuscular injection of 1,000,000 units of penicillin G, contained 1.67 μg. of penicillin per cubic centimeter. On the 11th day another pericardiocentesis yielded 110 cc. of similar material. Aqueous pencillin was instilled into the pericardial cavity.

When clinical and roentgenographic evidence of a right pleural effusion developed on the 14th day, aspiration revealed a purulent fluid, sterile on culture, with a protein content of 4.1 gm. %.

Gradually the patient gained strength, and the empyema, pulmonic infiltrate, and leukocytosis slowly dimished. After 34 days his temperature remained below 100 F, and he was discharged well on the 63d day.

Pneumonia Patients Excluded from the Phenoxymethyl Penicillin Program in 1956-1957.—Thirty-two patients whose blood and/or sputum yielded pneumococci were excluded from the statistics of the phenoxymethyl penicillin program. Two died within six hours of their initial dose of phenoxymethyl penicillin. Nine, treated with parenteral penicillin, had tuberculosis, congestive heart failure, or malignant lung disease so severe as to make the significance of the pneumonia and therefore the response to treatment difficult to evaluate.

The remaining 21 patients had pneumococcal pneumonia as the primary disease but could not be included because they either received no phenoxymethyl penicillin or received it in conjunction with another antibiotic. Six were treated with parenteral penicillin G because their pneumonia was complicated by shock, coma, or ileus. One of these responded satisfactorily; two died; 1 developed empyema but recovered, and two had prolonged periods of recovery.

Nine patients were inadvertently given other antibiotics by members of the resident staff. Four more, not given phenoxymethyl penicillin because of erroneous admitting diagnoses, were subsequently found to have pneumococcal pneumonia. One patient with penicillin sensitivity was given a tetracycline drug, and one, who was discharged against medical advice after 24 hours of phenoxymethyl penicillin therapy, was given intramuscular benzathine penicillin as he left the hospital. These 15 patients showed "satisfactory" responses.

TABLE 2.—*Results of Treatment of One Hundred Ten Cases of Pneumococcal Pneumonia with Phenoxymethyl Penicillin, 1955-1957*

		1955-1956	1956-1957	Total
Satisfactory, 95%	Excellent	33	59	92
	Submaximal	6	6	12
Unsatisfactory, 5%	Lived	3	1	4
	Died	0	2	2

Comment and Summary of the Two-Year Study

One hundred ten patients with pneumococcal pneumonia were treated with phenoxymethyl penicillin (penicillin V) at the Cincinnati General Hospital during the two-year period from October, 1955 to May, 1957. One hundred four (95%) showed a satisfactory response, and six (5%), two of whom died, showed an unsatisfactory response. All patients were classified as moderately (61%), severely (34%), or critically (5%) ill. Fifty-two per cent had one or more concomitant diseases, and twenty-seven per cent suffered from involvement of more than one lobe. Of the five critically ill patients, one died; two developed empyema; one, empyema and pericarditis, and two had a prolonged period of recovery. Of the 38 severely ill patients, 1 died; 1 relapsed, and 11 had prolonged periods of recovery. All 67 moderately ill patients recovered promptly.

The two patients who died, Cases 7 and 8, being in the older age group and debilitated by chronic disease, were unable to cope with severe infection. The prognosis in these two patients was poor from the outset, and it is doubtful whether any penicillin regimen would have saved them.

Case 9, who developed both pericarditis and empyema, deserves comment. The clinical "toxicity" associated with his pneumonia disappeared by the end of 48 hours of treatment. Nevertheless, pericarditis developed during oral phenoxymethyl penicillin therapy and pleural empyema while he was receiving 1,000,000 units of penicillin G every six hours intramuscularly! Neither of these purulent complications required surgical drainage.

Of the patients treated with parenteral penicillin G and therefore excluded from the statistics of the phenoxymethyl penicillin program, those with shock, coma, or ileus accounted largely for the treatment failures.

Thus those patients too ill to take oral medication would seem to do poorly on any penicillin regimen.

Oral phenoxymethyl penicillin has been shown to be an effective form of therapy for moderate and severe cases of pneumococcal pneumonia. Oral therapy avoids the pain of injection, the expense and effort of sterilizing needles and syringes, and the dangers of needle-borne serum hepatitis. Although phenoxymethyl penicillin is not recommended for those patients critically ill or having the purulent complications of pneumonia, it may be used with safety and confidence in the great majority of patients with pneumococcal pneumonia. The optimum dosage has not yet been established. Though our own patients were given 250 mg. every six hours, equivalent to approximately 1,600,000 units, patients in a similar series reported by Austrian and Winston[2] received the same dose at 12-hour intervals, with similar results. Because an occasional patient fails to absorb phenoxymethyl penicillin as well as most subjects, the larger dose may be a safer one.

Addendum

During the period October, 1957 through April, 1958, an additional 35 patients admitted to the Cincinnati General Hospital with pneumococcal pneumonia of moderate to great severity were treated with oral phenoxymethyl penicillin. The results were judged excellent in 28 (80%), submaximal in 6 (17%), and poor in 1. This patient developed a lung abscess, probably staphylococcal, distal to an obstructing bronchial mucous plug. Thus, of the 145 cases treated by this regimen over the three winter seasons studied, the results were satisfactory in 94.4% and unsatisfactory in 5.6%.

Miss Judith Carleton and Mrs. Naomi Turk provided technical assistance. The third-year study was carried out by Drs. James D. Michael and Doris Beatty.

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The Vasculocardiac Syndrome of Metastatic Carcinoid

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In the last few years, serotonin has emerged as a fascinating natural humor of the human body. Its myriad, miscellaneous, and mystifying functions are the delight and confusion of pharmacologists, the fascination and mystery of internists and surgeons, and the hope and bewilderment of psychiatrists and psychologists, as well as a phantom and will-o'-the-wisp for hematologists. The first clue about what we now know as serotonin appeared, but hardly emerged, about 90 years ago when Ludwig demonstrated that blood which had been defibrinated contained a vasoconstrictor principle not demonstrable in the same blood before coagulation. While most of the attention on the clotting mechanism traditionally focused on what had been taken out of blood in the process of clotting, here was a paradoxical situation—something had been added. Rapport and Page sought this mysterious vasoconstrictor and identified it in 1948. Thus 80 years elapsed between the discovery of a biological principle, known only by what it did, and the final identification and synthesis of the active compound serotonin, or 5-hydroxytryptamine, a derivative of tryptophan.

There are other converging lines of interest. The one which concerns the pharmacologists was highlighted by the brilliant studies of Erspamer. For many years he investigated an elusive vasoconstrictor material, which he got by extracting portions of the alimentary canal, particularly the mucosal surface. The material, which he called enteramine, turned out to be serotonin. Clotting experts demonstrated that platelets contain a great quantity of serotonin, which, however, seems to be picked up and carried around as cargo. Although it aids clot retraction, it has not been demonstrated to be an effective hemostatic agent. Little serotonin is found in the circulating blood, but it may appear in particular regions in sufficient concentration to cause local vasoconstriction. A possible harmful effect from locally released serotonin in myocardial infarction and pulmonary embolism has been suggested. On the basis of the intense vasoconstriction which occurs when large doses of serotonin are infused into experimental animals it is postulated that serotonin is important in regulating renal blood flow. Neurologists and psychiatrists are interested in the fact that in the central nervous system there are large amounts of serotonin. Hallucinations are produced by the dimethyl derivative of serotonin. Both central and peripheral effects of serotonin are blocked by lysergic acid diethylamide (L. S. D.), which produces effects like temporary schizophrenia. It has been suggested that the action of reserpine may be caused by its ability to reduce the power of the brain cells to hold on to serotonin. It then slips out of cells, where monoamine oxidase destroys it. Intracellular serotonin is not susceptible to this destructive power of monoamine oxidase. Thus a simple tryptophan derivative has many functions of a kind not even remotely suspected a few years ago.

Our own clinical interests now and in the past have crossed many of these converging lines, blending innocent fascination in a curious potpourri of vascular lesions [1-3] and flushes and flashes such as are said to vex our ladies. These have given rise to the vast and entertaining humeral mythology of the gynecologists. Work in the esoteric and

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frequently neglected domain of nutrition included a series of studies on tryptophan [4] and indole derivatives, hopefully designed to identify curious pigments excreted in the urine of pellagrins. This unpublished past work revealed that a major and toxic substance was indolacetic acid and that tryptophan was not toxic at all.[5] Studies on nicotinic acid and search for the precise molecule causing the flushing of the skin led to identification of this molecule in one of those masterpieces of clinical research which evoke a frantic outburst of interest and request for reprints—a total of three.[3] A long interest in matters of the heart, coronary sclerosis,[6-8] and aortic and other valve stenoses rounds out the background.[9] Along with Olch and Weinberg, one of us (W. B. B.) wrote about two patients with metastatic carcinoids and hyperserotoninemia and the dazzling cutaneous regalia of flagrant changes in skin with a harlequin masquerade of colors [10] said to "mimic in clinical miniature the fickle phantasmagory of the Aurora Borealis." A third patient whom we had under observation helped us conduct a number of observations and studies. These are the subject of this paper.

The Patient's Story

This tale concerns the long and vexatious trials of a man we first observed when he was 57 years of age. The first inklings of any serious difficulties began about nine years before we saw him, when he was troubled with hemorrhoids and intermittent diarrhea. Two years later, he had an automobile accident in which he was not badly hurt but was shaken up. He remembered this mishap well, and in his mind it was the start if not the cause of his woes. From this epoch onward he was distressed with irregular comings and goings of an indescribable kind of nervousness. The occasional diarrhea he had earlier recurred more frequently but not in any regular association with the attacks of anxiety and nervousness. He was a railroad telegraph operator, and no doubt he sent rather peculiar and interesting messages, because he became easily excited and flustered whenever he addressed himself to even the simplest problem. At such times, he felt warmth in the neck and face, along with lightheadedness and nervousness. Thinking was difficult. In a very unpleasant situation, he would get cramping abdominal pains, sometimes severe enough to require his doctor to inject narcotics. Three and one-half years before admission these troubles had gotten so bad that he had x-rays of the alimentary canal which revealed "spastic colitis and diverticulitis." No benefit accrued from a special diet, antispasmodics, antibiotics, and other preparations. During the seven years before admission he had lost 40 lb., only 8 of them during the previous eight months. He had had no respiratory distress, palpitation, bronchial spasm, or symptoms suggesting heart disease. During the time he was under observation, from March 22, 1955, to the time of his death, on July 11, 1956, with two admissions to the Iowa City V. A. Hospital and two admissions to the University Hospitals, his complaints continued and additional ones appeared. Physical examination revealed a man quick in movement and in speech. He had lost weight. Hair was gray and silky. His skin was warm and of fine texture, with tiny telangiectases over the torso, head, neck, and upper extremities. The complexion was fair and persistently ruddy. Superimposed on the florid hue was a transient waxing and waning of erythema in blotchy patches around the face and neck. This grew more spectacular as time went on. Other significant items in the physical examination were a fine tremor of the tongue and the outstretched fingers, an inconstant lid lag, an accessible but not enlarged thyroid

Fig. 1.—Patient during period when his face was flushing and the skin of the chest was very little changed.

Fig. 2.—Two minutes after Figure 1, showing the reduction in facial flush and the flush developing in the upper sternal area. An angioma is visible on the right shoulder.

Fig. 3.—Gross section of the liver, revealing multiple metastases.

Fig. 4.—Microscopic section of the liver, revealing the carcinoid tumor and some compressed liver tissue; reduced 35% from mag. × 132.

Fig. 5.—The primary lesion in the ileum and the extension and metastases to the mesentery. Primary tumor is on the left.

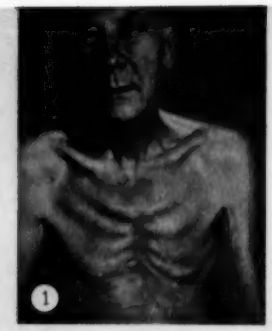
Fig. 6.—Microscopic section of the primary tumor in the ileum; × 42.

Fig. 7.—A close-up of the skin, revealing the mottled areas of pallor, erythema, and cyanosis. Small angiomas may be made out.

Fig. 8.—Angiomatous lesion of the skin revealing dilated, thin-walled blood vessels and vascular channels.

Fig. 9.—Gross appearance of tricuspid valve, revealing the abundance of gelatinous tissue with many high lights.

Fig. 10.—Tricuspid valve, revealing extensive proliferation of fibroblasts and much amorphous ground tissue covered by a thin endothelial layer; reduced 35% from mag. × 79.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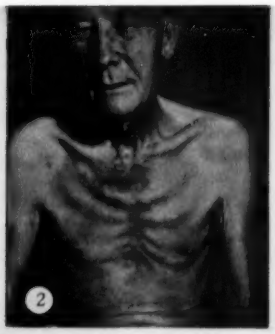
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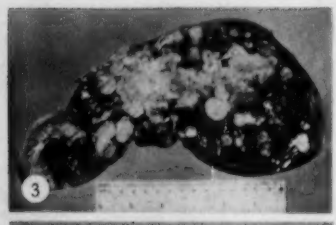
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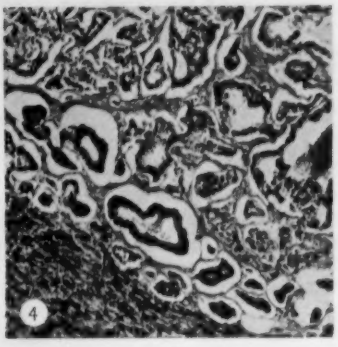
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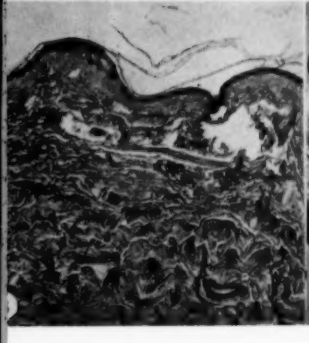

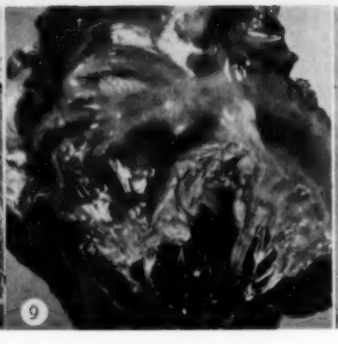
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gland without bruit, and a somewhat labile blood pressure recorded within a few minutes at 188/106, 164/96, and 130/70. There was no cardiac enlargement, murmur, or suggestion of heart failure. There was slight enlargement of the liver and of the prostate gland.

The number of stools decreased when he was treated with camphorated opium tincture (paregoric) and bismuth. Psychological tests were interpreted as indicating that he suffered from "pressure from inner tensions. . .flightiness of ideation. . .the total picture suggests a sharply increased drive." Psychiatrists called the situation "chronic brain syndrome without psychosis but demonstrating neurotic reaction" and recommended chlorpromazine, 25 mg. three times a day. This was increased gradually to 200 mg. a day. He was discharged to the care of his physician. Treatment brought no improvement.

He was seen next on Feb. 3, 1956, in the medical service of the University Hospitals, where he arrived with a tentative diagnosis of ulcerative colitis and involutional melancholia. During the interim there had been little change until early in October, when he had severe sharp stabbing abdominal pain to the right of the umbilicus, requiring narcotics. This had recurred four times and was attended by vomiting. The diarrhea persisted. He noted a "rash," had insomnia, and lost 21 lb. more.

Physical examination revealed a cachectic man 6 ft. tall, chronically ill but alert. He was not bedfast. His skin had a peculiar color. It was blotchy, some areas being erythematous, other purplish, and others pale with a silvery shimmer. The blotches were not elevated or indurated. The color blanched with pressure. The only other change was the gross enlargement of the liver. The lower border descended below the umbilicus with inspiration. It was irregular and tender. Pressure on the liver caused a fit of flushing. No abnormalities were found in the heart or lungs.

Hospital Study and Therapy.—Skin biopsy revealed only trivial chronic inflammatory changes. Sigmoidoscopic examination revealed normal mucosa. He was seen in consultation with the surgeons. Exploratory operation was advised in view of the likelihood of low-grade intestinal obstruction manifested by the cramping abdominal pains and obstruction to the barium in the mid-portion of the descending colon found on two x-ray studies.

On March 20, 1956, an exploratory laparotomy revealed a 4-5 mm. intralumenal nodule in the upper ileum. It extended through the wall of the bowel, invading the mesenteric nodes and completely encircling the celiac axis. There were extensive metastases in the liver. Manipulation of the tumor mass about the root of the mesentery twice resulted in a profound but transient drop in blood pressure to 50-70 mm. Hg systolic. No obstruction was found in the colon, spasm having vanished with anesthesia. Biopsy of a metastatic nodule in the liver revealed the characteristic picture of malignant carcinoid. The postoperative course was uneventful. A low-grade fever, ranging from 99-101 F rectally, persisted throughout the hospital course. He was discharged on April 9, 1956.

His next admission was one month later because of the development of paroxysms of loud and painful hyperactive peristalsis. They were initiated by eating and were proportional to the volume of food ingested. The low-grade fever was unchanged. Weight had risen from 125 lb. to 145 lb. Dependent edema presumably accounted for the weight gained. For the first time a soft systolic murmur was heard along the left sternal border. Bronchial wheezes were heard at times.

Hospital Course and Therapy.—Abdominal pains, vomiting, increasing edema, and psychotic behavior were the major problems. Symptomatic therapy was of only slight benefit as he continued to worsen. His psychotic behavior was mainly that of reacting to auditory and visual hallucinations of a paranoid nature. He was transferred to the Iowa City V. A. Hospital on June 22, 1956, for terminal care.

By now he had become too weak to care for himself. He was disoriented. Ascites had developed as well as edema of all portions of the body. There were bilateral pleural friction rubs. Blood pressure was 125/85-80 in the right and 135/85-80 in the left arm in the supine position. The heart was of normal size, rate, and rhythm. The sounds were natural, with the aortic second sound being louder than the pulmonic second sound. There was a Grade 1 apical systolic murmur and a similar murmur over the aortic and tricuspid valve areas. These were not prominent, and we thought they might result from the anemia (Hgb., 9.7 gm. %). There were no gallops, shocks, or thrills and no diastolic murmurs. The abdomen was distended with fluid. After diuresis a hard, enlarged, visibly knobby liver was again apparent. There was no distention of the veins in the neck. The cutaneous color changes were becoming more and more marked, the brighter, redder hues predominating over the upper portions of the body and the bluer, darker hues over the lower extremities. There were no changes at any time which resembled the skin lesions of pellagra,[11] but dark, blackish-purple, flat angiomas appeared. They were most numerous on the front of the chest and the dorsal aspect of the upper arms. The individual angiomas ranged in size from specks just visible to those 2-3 mm. in diameter. They blanched on pressure. The structure of the lesion is revealed in Figure 6. In addition, there were numerous networks of fine

Test Results of Patient with Vasculocardiac Syndrome of Metastatic Carcinoid

	March 22-May 31, 1955	Feb. 3-April 9, 1956	May 11-June 22, 1956	June 22-July 11, 1956
Stool				
Blood	Trace (Guaiac)		Trace (Meyers)	
Parasites	None	None		
Pathogenic bacteria	None	None		
Solids, %/24 hr.	17 (normal)			
Fats, % of total solids	19 (normal)			
Thyroid function				
B. M. R., %	—4			
PBI, μg/100 ml.	4			
I^{131} uptake by thyroid, % of administered dose				
1 hr.	6.6			
4 hr.	10.0			
6 hr.	11.4			
24 hr.	20.2			
I^{131} present in serum as thyroxin at 24 hr., %	0.7			
I^{131} excreted in urine during 1st 24 hr., %	38.6			
Gastric acid without stimulation, %	46			
ECG	Essentially normal	Minor T-wave abnormalities		ST segment depression; T-wave flattening; prolonged QT.
EEG	Suspicious EEG but not clearly focal			Grossly abnormal; no normal activity; diffuse slow activity at 2-5/sec.
Radiographic & fluoroscopic studies	Healthy chest Normal I. V. P.; small sinus tract in posterior urethra; 1+ BPH; normal stomach & duodenum; probably normal small intestine, emptied in 3 hr.: diverticulosis of sigmoid colon	Healthy chest Normal stomach, duodenum, & small intestine; obstruction to retrograde flow of $BaSO_4$ on 2 attempts at Ba enema	Healthy chest Normal stomach, duodenum, & small intestine, with rapid transit time, a large amount of barium reaching sigmoid colon and rectum in 1 hr. and 45 min.	Healthy chest (no change in heart size, no vascular enlargement or infiltration or pleural fluid)
WBC/mm.³	11,600	11,400	13,650	10,350
Differential count, %				
Bands	2		1	2
Segmented neutrophils	57	55	62	63
Lymphocytes	38	32	30	29
Monocytes	3	13	4	6
Basophils	1		1	
Eosinophils			2	
RBC/mm.³			2,580,000	
Hemoglobin, gm/100 ml.	12.3	11	8	9.6
Hematocrit, %		33	28	31
Platelet count/mm.³		712,000		
E. S. R., mm. in 1 hr.	35 (Cutler)	101 (Westergren)	88 (Westergren)	51 (Wintrobe) 22 with correction for hematocrit
Bleeding time, min.		3½		
Clotting time, min.		4		
Prothrombin time, sec.				
Patient	21	18.8		
Control	11	14.8		
BUN, mg/100 ml	20	16	28	72
Blood Creatinine mg./100 ml.	1.1	1 2	1.8	1.1
Serum				
Sodium, mEq/L.	135			135
Potassium, mEq/L.	4.7			3.5
Chlorides, mEq/L.	109			98
CO_2, mEq/L.	23			31.5
Calcium, mg/100 ml.				9.3
Total protein, gm/100 ml.	7.2	7.0	5.4	7.8
Albumin, gm/100 ml.	5.0	3.5	2.8	3.7
Globulin, gm/100 ml.	2.2	3.5	2.6	4.1

Phosphatase, Bodansky units				
Alkaline		4.8	7.6	1
Acid		0.6		
Cephalin flocculation				
24 hr.	0			
48 hr.	1+			
Thymol turbidity, units				1 2
BSP retention at 45 min., %	9	11	12	
Urine				
Color	Straw		Dark amber	Straw
Sp. gravity	1.022	1.022	1.018	1.015
pH	4.5	5.5	5.5	5.5
Prot. (qual.)	0-2+	0-3+	0-tr.	0
Sugar (qual.)	0	0	0	0
Hgb.		0	0	
Bile			1+	
Microscopic	7-9 WBC/hpf; few WBC clumps; occas. long narrow hyaline cast	2-3 WBC/hpf loaded with hyaline & granular casts	15-20 WBC/hpf	30-40 WBC/hpf; 0-2 RBC/hpf; few WBC clumps; occas long narrow hyaline casts
Urine culture	No growth			
Porphyrin abnormalities in urine		None		
PSP excretion, %				
15 min.	24			
60 min.	62.5			

telangiectatic vessels widely disseminated over the skin.

Salt restriction and diuretics were successful in clearing the edema, but vomiting became more of a problem. At one time the vomit was feculent and gastric aspiration was necessary. Just before death he became more disoriented and used to refer to himself in the third person. Paralysis of the superior rectus muscle of the left eye and a friction rub over the liver developed. He died quietly on July 11, 1956.

Autopsy.—At autopsy the principal abnormalities consisted of a small discrete yellow-gray nodule in the wall of the proximal ileum with gross metastases to the regional lymph nodes and the liver, which was almost entirely replaced by nodules and masses of tumor tissue. Although the heart was smaller than usual, the right ventricle was moderately hypertrophied. The tricuspid and pulmonic valves were thickened, rubbery to the touch, shimmering with increased high lights, and somewhat succulent. They were not stenotic. There was no septal opening between the atria or the ventricles. The mitral and to less degree the aortic valve had a similar lesion. The coronary arteries were almost occluded by calcified atherosclerotic plaques, but there was no myocardial infarct. There was much ascites and bilateral hydrothorax. Other findings were acute esophageal and duodenal ulcers, testicular atrophy, acute passive congestion of the right lung, and aortic sclerosis. The tumor nodules microscopically had the structure of an argentaffinoma (carcinoid tumor). An analysis of the tumor in the liver by Dr. Sjoerdsma revealed that it contained 88μg. of serotonin per gram. Normally there is none in the liver. There was intense fibrosis in the postoperative abdominal adhesions, far out of proportion to the usual amount. Sections through the tricuspid and pulmonary valves disclosed a cartilage-like proliferation of connective tissue with no calcification.

Special Studies.—We did special studies of the 5-hydroxyindolacetic acid (5-HIAA) excretion in the urine and of blood coagulation and assay of serotonin in the platelets. We used two serotonin antagonists to judge possible clinical and metabolic effects. During the first admission to the University Hospitals, spot checks of the urine revealed strongly positive tests for high 5-HIAA and a 24-hour specimen contained 665 mg., while the normal range is from 2-9 mg. After he recovered from the operation, we gave him an antiserotonin (BOL 148), two tablets five times a day for four days. There was no change in the signs or symptoms. The 5-HIAA excretion in 24 hours varied from 195 to 921 mg., as it had before this therapy. When he was next admitted to University Hospitals, we gave him another antiserotonin preparation, 1-benzyl-2-methyl-5-methoxytryptamine HCl, 25 mg. three times a day for two weeks. There was no apparent clinical effect. The 5-HIAA excretion in 24 hours did not change from its previous erratic variations, ranging from 250 to 595 mg. during or after therapy. Serotonin analysis of platelets gave values of 1.3μg. of platelet nitrogen (normal values by the method are 0.3 to 0.5μg.

A great many studies of blood coagulation were done. 1. There was no abnormality of blood coagulation. 2. Platelet-deficient plasma from the patient produced no improvement in the defective prothrombin consumption of a patient with severe thrombocytopenia. 3. Serum from the patient caused no more improvement than a normal control in correcting defective prothrombin consumption of the same thrombocytopenic patient. There was a slight but not significant increase in the speed of clot retraction.

It is probable that Steiner and Voerner were the first to describe the clinical entity of metastatic carcinoid, in 1909, in their paper entitled "Miliary Angiomatosis." Their patient, a 27-year-old man, suffered from severe flushing of the face and trunk. He was literally covered with generalized telangiectasia. A specimen of skin contained telangiectases, thrombosis of large dilated vessels, and formation of new vessels. This patient was under observation for five months. Dr. Parkes Weber tells me that this man's hospital records were destroyed by bombing in World War II. Despite this and several other definite or probable cases, this syndrome emerged only recently.

Comment

Our patient had a flamboyant hot flash, one that can be seen as well as talked about. It is hard to understand how such a spectacular show could have waited so long for clear delineation. The full syndrome has had attention only recently. Three groups independently reported cases: first, from Milwaukee, Rosenbaum, Santer, and Claudon,[12] in 1953; then, from Zurich, Isler and Hedinger, in 1953,[13] and then, the fullest report, from Uppsala, by Thorson, Biörck, Björkman, and Walderström, in 1954.[14] In a detailed and thoughtful review, McKusick[15] summarized the rapid advances in our understanding of the disorder and abstracted the most recent case reports, which now are rolling off the presses in a steady drumfire. McKusick has likened the situation to a Jules Verne romance, rather than to the outrageous lies of Baron Munchausen. To me its fantastic exaggeration is rather that of Paul Bunyan.

There are a few additional observations which are worth mentioning. A very detailed case report of a probable case was made by Arnett and Long in 1931, though they were of the opinion that the tumor arose in the pancreas. We have seen no reference to Wrightson's case, notable for the metastasis of the carcinoid to the heart as well as the liver. The sparse clinical details record only chronic diarrhea. Jones reported a 52-year-old man with a milder degree of the carcinoid syndrome who did not have any visible metastases to the liver, which was examined at two operations. The urinary excretion of 5-hydroxyindolacetic acid was five or six times normal. It fell to normal after a large retroperitoneal node of carcinoid tissue was resected. It is probable that this man was delivering serotonin to the inferior vena cava, by-passing the liver. Harrison, Montgomery, Ramsey, Robertson, and Welbourn described a 55-year-old woman with the clinical features of Cushing's syndrome with a primary bronchogenic tumor with extensive hepatic metastases who had flushing, bronchospasm, and some elevation of 5-hydroxyindolacetic acid in the urine. At autopsy the adrenals, pituitary, and heart valves were normal.

We shall merely mention a few of the well-recognized features and still unsolved mysteries of the syndrome. *Diagnosis* is easy when the full syndrome is present with the characteristic vasomotor, angiomatous, bronchoconstrictor, hyperperistaltic, metastatic, and cardiodyspastic manifestations. The Udenfriend test[16] for 5-HIAA in the urine is simple and apparently specific. In many hundreds of tests we have found no strongly positive tests except in patients with metastatic carcinoid. The test was negative in two persons with carcinoid of the bowel without metastasis, though this may not always be true. Normally the liver or the liver and lungs inactivate, sequester, or destroy most of the serotonin.

Flushing, with a curious triple reaction, may be caused by a vasoconstrictor agent by (1) release of histamine, (2) stimulation of peripheral vasomotor nerves, (3) local reactions aiming at restoring a steady state, or (4) something else. We do not know whether the regional effector mechanism or

local factors are important, since the pattern of most intense flushing repeatedly recurs in precisely the same place and shape, fading into variations on a constant theme. Release of serotonin by massage of the liver triggers the effect with the precision of a circulation-time test.

Bronchial spasm, which may be induced in experimental animals, presumably accounts for the "asthma" of which the patients complain. It is paroxysmal, rarely provoked by exertion till late in the disease. Larger rather than small branches of the bronchial tree seem to be implicated.

Hypermotility of the intestine and a plentiful watery diarrhea molest the victims of this disorder. Clifton and his colleagues [17] have demonstrated a sharp contraction of the bowel in normal persons after intravenous infusion of serotonin, a reaction not shared by persons with cirrhosis of the liver or sprue. The diarrhea thus probably is another humoral effect rather than a result of the primary lesion in the ileum.

Antagonists to serotonin were suggested as possible agents for treating patients with hyperserotoninemia.[10] We had no luck with them in this patient, though other observers have found some abatement of symptoms and decrease in urinary excretion of 5-HIAA. Many speculations are suggested about effect on tumor growth of a substance which antagonizes the function of product of the tumor, but we know little.

Acquired valvulitis we believe is caused by the repeated injury done to the valves particularly of the right side of the heart. The intermittent but frequent surges of high concentrations of serotonin reaching the right side of the heart, which may be undergoing invisibly the same vascular torment which plagues the skin, may damage vessels and endothelial surfaces alike. Spasm and reactive hyperemia in a structure whose mission leaves little repose gives rise to inflammation, fibroblastic reaction with an abundance of amorphous ground substance, and ultimate scarring. Valves whose inflamed surfaces are in brief contact grow together to produce stenoses. Some small effect in the valves of the left heart, in our man who had no leaks between right and left side of the heart, suggests that the capillary bed of the lung could not clear the blood of serotonin when it gushed out of the liver in large quantities. The proliferative valvulitis leading to ultimate stenosis has raised much interest, but we are far from understanding the mechanism of its production. Fatigue and exhaustion of blood vessels and other smooth muscle may injure the lining membranes. Platelet thromboses, endocardial or within the vessels of the valves, has been blamed. By analogy with plant-growth hormones, serotonin might cause proliferation of connective tissue and ground substances, leading to dense scarring and stenosis. This is a guess.

Angiomas arise in the skin. These are unlike spiders, cherry angiomas, or venous stars [1,2] but more like venous lakes,[18] though smaller and having a completely different distribution. Figure 11, sent to us by Capt. Davis, discloses the appearance of an angioma of the skin. The histopathology suggests angiomatous and telangiectatic change, proliferative and degenerative. The analogy with spiders and the role of the liver in excreting, inactivating, or destroying estrogens [1] are in keeping with the fact that ordinarily the carcinoid tumor must have metastasized to the liver to produce the syndrome.

Tryptophan metabolism is impaired in that the avid carcinoid tumor seems to have high metabolic priority for this precursor of serotonin. There is no evidence that nicotinic acid metabolism is impaired. We have not seen pellagra in our three patients. If it occurs, we would ascribe it to the losses of vitamins from hypermotile diarrhea.[19]

Clotting is active, and retraction is excellent, as judged by studies of our patient. In fact, intravascular clotting may be a factor in the valve lesions and angiomas. No supernormal clotting appears, though the clot may retract excessively. The notion of an analogy between contraction of the pro-

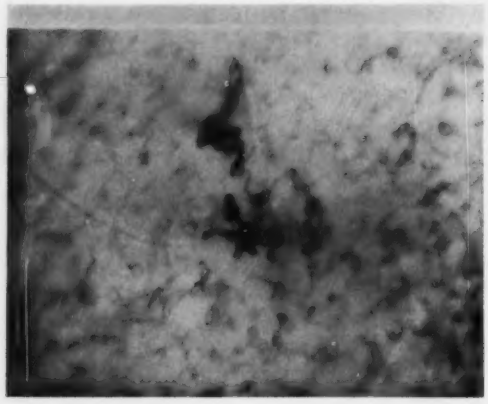

Fig. 11.—Angiomas appearing in the skin in a patient with carcinoid metastasizing to the liver. Reproduced through courtesy of Capt. Davis, Walter Reed Hospital, Washington, D. C.

tein fibrin and the protein in smooth muscle has been suggested, but identical physical processes have not been demonstrated. Platelets, which do not make serotonin, carry it around as cargo, but why is uncertain.

Fibrosis of the adhesions from the abdominal operation was very dense and hard. This reaction and the general increase in collagen, fibrinoid, and hyaline material suggest speculations about the pathogenesis of such diverse diseases as cirrhosis of the liver and systemic lupus erythematosus.

Conclusion

We have presented another patient with the vasculocardiac syndrome caused by hyperserotoninemia produced by a metastatic carcinoid tumor in the liver. Speculations, which are approaching close to clinical certainty, indicate that the physiologic disorder is smooth muscle spasm most violent in blood vessels, skin, heart valve, and bowel. Repeated insults over a period of years disorganize the structure of these organs while the function is still suffering under the blows and buffets of this powerful humor. The many functions of serotonin are beginning to be explored along lines with much interest and enchantment for the clinician. What was an unheard of syndrome became rare and will perhaps turn out to be merely uncommon. Even so, this unusual syndrome may throw light on a host of common diseases and everyday functions in health.

Post Script

This man was addicted to moanin',
Confusion, edema, and groanin',
Intestinal rushes,
Great tricolored blushes,
And died from too much serotonin.

Drs. Udenfriend and Sjoerdsma and their associates in the National Heart Institute at Bethesda helped with the assay of urine, platelets, and tissue; Dr. William Jolly made numerous studies of the clotting mechanism, and Dr. J. C. Kosek helped to set up the test for 5-HIAA during his third and fourth years as an undergraduate medical student in the College of Medicine.

University Hospitals, State University of Iowa.

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Chronic Renal Disease with Secondary Hyperparathyroidism

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Since the observations of Lucas, in 1883,[1] it has been known that abnormalities of the skeletal system occur in patients ill with chronic renal disease. These include rickets, osteomalacia, osteoporosis, osteosclerosis, and osteitis fibrosa.[2-6] Osteitis fibrosa occurs only in association with primary and secondary hyperparathyroidism. It was, therefore, surprising to find on reviewing the literature very few well-documented instances of renal disease with secondary hyperparathyroidism, i. e., with osteitis fibrosa and significant enlargement of the parathyroid glands. In this paper we report the clinical and pathological features of renal disease with secondary hyperparathyroidism in 17 patients. In addition, the 25 cases reported in detail in the literature are reviewed and the important clinical and pathological features are discussed.

At the present time reliable chemical or biological methods for the assay of parathyroid hormone in blood do not exist. In the absence of such a method, we have made the diagnosis of hyperparathyroidism in patients ill with chronic renal disease when there was evidence of the effects of increased parathyroid hormone secretion on the skeleton, i. e., when there was osteitis fibrosa. All patients discussed in this paper had postmortem evidence of (1) chronic renal disease, (2) significant enlargement of two or more parathyroid glands, and (3) osteitis fibrosa—a bone lesion which pathologists consider to be specific for hyperparathyroidism.[7-10]

One of the patients was studied in detail, and her case history is reported below.

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Report of a Case

An 18-year-old woman entered the hospital with severe azotemia, anemia, and widespread osteitis fibrosa cystica. The differential diagnosis between primary renal disease with secondary hyperparathyroidism and parathyroid adenoma with secondary renal disease presented some difficulty. However, severe chronic pyelonephritis was diagnosed by renal biopsy. The patient died of uremia 11 months later, by which time the osteitis fibrosa had progressed even further. Post mortem, all four parathyroid glands were greatly enlarged; the diagnosis of osteitis fibrosa cystica was confirmed, and small congenital polycystic kidneys with severe, acute, and chronic pyelonephritis were found.

An attractive 18-year-old white schoolgirl was first admitted to the University of Illinois Hospitals on Nov. 5, 1954. One month previously, while on vacation in Canada, she developed pain in the left flank, partially relieved by lying on the right side. It recurred intermittently for six hours and was followed by vomiting for three days. It was not

accompanied by fever or chills, and she had no hematuria and passed no stone. She was advised to enter the hospital for investigation.

Her birth and early development were normal. She had recurrent sore throats until the age of 7 years, when her tonsils were removed, but at no time did she have hematuria. At this age she had generalized body pains and a diagnosis of rheumatic fever was made by her physician.

At the age of 10 her school teacher noticed frequency of micturition, and the patient complained of burning and urgency on urination. These symptoms, diagnosed as pyelitis, continued for four to six months and then subsided. Although her physical development progressed normally thereafter, a definite change was noted by both teachers and parents. Whereas previously she had always been a very active child, she began to complain of being exhausted, seemed to lack vigor, and was unable to take part in games at school.

At the age of 14 years she was found to be anemic; the anemia failed to respond to any form of treatment. A short while later polyuria and increased thirst were noticed, and at the age of 16 she was told she had proteinuria. At this time she began to have recurrent epistaxis. One year later, she observed that the hair was receding from her forehead and that the shape of her fingers was changing.

In the last year before her admission to hospital she lost 5 kg. in weight; she complained of increasing fatigability and weakness and began to have cramps in the calves and abdominal muscles. These symptoms were not relieved by an appendectomy in January, 1954. There was no family history of kidney or of parathyroid disease.

Physical Examination.—She was a young woman, alert and in no immediate distress. Her height (143.2 cm.) and sexual development were normal. She was thin and pale and had obviously lost weight (43.75 kg.) There was a striking loss of hair from the forehead. The terminal phalanges of all fingers were bulbous and resembled clubs; they were thickened and shortened, but there was no softening of the nail bed and no thickening of the subcutaneous tissues (Fig. 1). Similar but less marked changes were noted in the toes. Both frontal bones were prominent and slightly bossed. The upper and lower jaws appeared to be slightly thickened, but the teeth were normal.

Fig. 1.—Photograph of the fingers of the right hand. Note the thickening and shortening of the terminal phalanges, which resembled clubs.

The temperature was normal; the blood pressure was 140/80 mm. Hg; the pulse rate was 90 per minute, and the pulses were of good volume. There was a remarkable thickening and hardness of all the palpable arteries. The heart was normal in size. The heart sounds were of good quality, and the pulmonic second sound was louder than the aortic. A soft blowing systolic murmur was heard over the precordium. Findings on examination of the lungs and abdomen were within normal limits. No abnormality was found on examination of the neck, and neither thyroid nor parathyroids were felt. There was a slight narrowing and tortuosity of the retinal arterioles, but hemorrhages, exudates, and papilledema were not seen. The muscles and peripheral nervous system were normal, and Chvostek's and Trousseau's signs could not be elicited.

Laboratory Investigations (Table 1).—Hematocrit, 23%; hemoglobin, 7.5 gm/100 ml.; leukocyte count, 6,700 per cubic millimeter; differential count, normal. The anemia was normochromic and normocytic. The pH of the urine varied from 5.5 to 7.0; the urine contained protein 3+, no glucose, and no acetone; occasional leukocytes, and hyaline, granular, and cellular casts were found in the centrifuged specimen. The urine specific gravity ranged from 1.006 to 1.010, which figure was never exceeded. Enterococci and micrococci were cultured from the urine on two occasions, but other urine cultures were sterile. Details of the alterations in blood chemistry and renal function are given in Table 1.

An x-ray of the heart and an electrocardiogram were normal. No dye was excreted when an intravenous pyelogram was made, and in a retrograde study the pelves and calyces were normal. The kidneys appeared to be normal or slightly smaller than normal.

X-rays of the bones revealed decalcification of the entire skeleton, with alteration of the spongiosa and trabecular pattern. There was well-marked resorption of bone in the distal phalanges of the hands and feet and demineralization of the remaining osseous structures (Fig. 2). Pseudocystic changes were noted in the left fourth metacarpal bone and distal end of the radius. There was subperiosteal resorption in the proximal shaft of the humerus and the long bones of the hands. The skull (Fig. 3) and bony thoracic cage were demineralized. The distal end of each clavicle was decalcified. The lamina dura was completely absent. Calcification was observed in the vessels of the

TABLE 1.—*Laboratory Investigations in Patient*

Date	Hematocrit	Serum												Renal Function
		Creatinine *	BUN *	N. P. N.*	Ca *	PO_4 †	Alk. Phos.†	Na ‡	K ‡	Cl ‡	CO_2 ‡	Albumin ‖	Globulin ‖	
First Hospital Admission														
11- 7-54	23		117	143	9.9	8.5	13.6			107	19	5.2	1.9	S. G. conc., 1.006
11-15-54		7.6		177	9.7	9.4	9.4	140	4.7			4.3	2.1	Urea clear., 6.2% A. N. R. F.
11-30-54	33	6.9	109	140										Creat. clear., 6.8 ml/min.
12- 7-54					10.3	8.3		135	6.1	94	25	5.2	2.8	PSP, <2% in 15 min.
12-14-54	37	6.9		177		7.9		142	5.2	99	23			Protein, 3+ WBC, casts
At Home Clinically Improving: Dietary Protein 40 gm.; P 800 mg.; Na 800 mg.														
12-23-54	31	7.6	113	130	9.5	7.4			5.8	102	23			
2- 3-55	23	7.2	79	102	9.6	6.7		147	5.2	112	21			
3-24-55	31	9.2	109	128	9.7	6.8		147	5.0	107	22			
At Home Clinically Deteriorating: Development of New Bone Cysts														
5-19-55	22			183	9.9			132	4.8	95	20			
6- 9-55	26	10.4	142	166	9.1	9.0	10.9	144	4.5	87	30			
Second Admission to Hospital														
6-23-55	21			160	9.7	7.4		139	4.7	90	22			S. G., 1.000-1.010; protein, 4+; RBC, WBC, casts; fat. PSP, 0% in 15 min.
At Home: Severely Ill														
8- 4-55		15.6	131	190	9 9	6.3		141	5.2	104	16			
Final Hospital Admission														
9- 1-55		15.7		268	8.4	9.5	16.4	116	4.9	77	17			S. G., 1.008-1.010; Protein, 3+; WBC; casts
9-10-55	34			252				125	4.1	90	14			
9-22-55		16.8		284	7.6	8.3		137	4.8	102	8			

* Mg/100 ml.
† Bodansky units.
‡ mEq/L.
‖ Gm/100 ml.

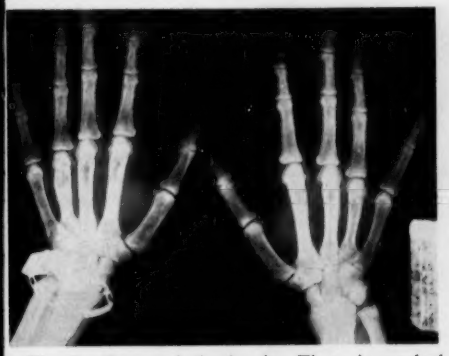

Fig. 2.—X-ray of the hands. There is marked demineralization and widespread subperiosteal bone resorption in the shafts of the long bones, seen particularly well in the middle phalanges. The terminal phalanges are severely involved. Pseudocystic changes are observed in the left fourth metacarpal bone.

Fig. 3.—X-ray of the skull, showing diffuse demineralization and a "ground glass" appearance. The lamina dura is completely absent.

pelvis and both feet. The radiological diagnosis was hyperparathyroidism, probably secondary to renal disease. A barium swallow showed slight displacement of the column of barium to the left at the pharyngoesophageal junction. It is of interest to note that the patient had fallen and hurt her knee in December, 1953, one year before admission to hospital. The x-ray revealed no fracture, but when the films were reviewed subperiosteal absorption of the anterior surfaces of the femoral shafts and the medial surfaces of the tibiae was seen. The trabecular pattern was altered, and there was demineralization.

All observers agreed that the patient had hyperparathyroidism. Although most felt that this was secondary to long-standing renal failure, some thought that the hyperparathyroidism was primary and that severe renal involvement was the consequence of primary parathyroid disease. Owing to lack of cooperation, calcium-balance studies were unsatisfactory. A renal biopsy was made on Nov. 30.

Renal Biopsy (Fig. 4).—Most of the 17 glomeruli were completely hyalinized. In the remainder the glomerular tufts were essentially normal, but there was very severe periglomerular fibrosis. Many tubules were replaced by fibrous tissue. Most of the surviving tubules were markedly atrophic, but a few were moderately dilated and contained abundant proteinaceous material. The lining cells were somewhat swollen. The interstitial fibrous connective tissue was very greatly increased and contained numerous foci of chronic inflammatory cells and a few small deposits of calcium. The small arteries were thickened and fibrotic. Culture of the renal tissue was sterile.

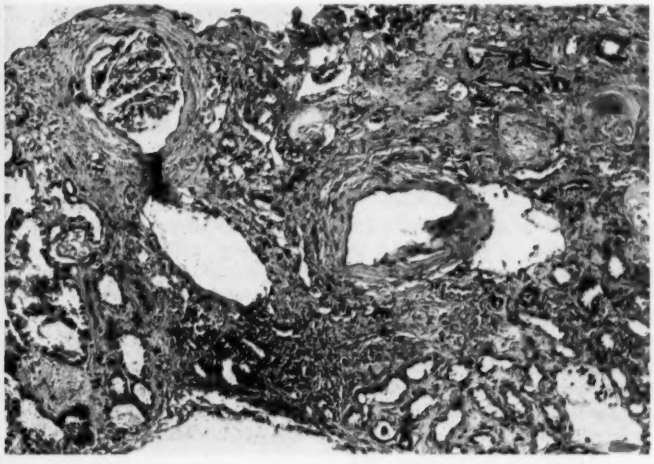

Fig. 4.—Renal biopsy specimen. Note the severe interstitial fibrosis. The interstitial tissue is infiltrated with chronic inflammatory cells. Most of the tubules have been replaced by fibrous tissue. Only one glomerulus can be identified in this field; it is surrounded by well-marked periglomerular fibrosis. Hematoxylin and eosin; reduced 40% from mag. × 140.

Diagnosis.—The diagnosis was chronic pyelonephritis of severe degree. None of the changes associated with primary hyperparathyroidism were found. The findings on renal biopsy supported the diagnosis of primary renal disease, viz., long-standing pyelonephritis, and suggested strongly that the bony manifestations were due to secondary hyperparathyroidism.

A diet containing 40 gm. of protein, 350 gm. of carbohydrate, 100 gm. of fat, 800 mg. of phosphorus, and 35 mEq. of sodium was prescribed. She was given supplementary calcium carbonate, 3.8 gm. daily, and was instructed to drink a large volume of water. The hematocrit rose to 37% after transfusion of 1,500 ml. of blood. There had been little change in the patient's condition when she left the hospital on Dec. 18. She still complained occasionally of cramps in the calves and abdominal muscles, but at no time had she had tetany.

She was observed in the outpatient department. Table 1 gives details of the biochemical investigations. In January, 1955, she felt much better and was leading a moderately active life. She was not short of breath; the pains in the calves had disappeared, but she complained of persistent dull pain over the left pubic ramus. She was tender at this site, and well-marked bone resorption was seen on x-ray. The blood pressure was 165/105 mm. Hg, and there was slight edema of the ankles.

In February, she felt and looked better than for many months. The N. P. N. had fallen to 102 mg/100 ml., and the BUN to 79 mg/100 ml. In April, she became short of breath on exertion; the blood pressure was 160/110 mm. Hg, and there was radiological and electrocardiographic evidence of left ventricular hypertrophy. There was no change in the radiological appearance of the hands. The serum creatinine had risen to 9.2 mg/100 ml., and the N. P. N., to 128 mg/100 ml. The serum inorganic phosphorus had fallen to 6.8 mg/100 ml. As she was unable to tolerate the severe dietary restrictions, the protein was increased to 50 gm. and the phosphorus to 1,000 mg. per day. In May, she noted the appearance and rapid growth of swellings in the left and right nasolabial region and in the right second toe. The expanded maxillary bones could be palpated bimanually.

Second Admission to Hospital.—The patient was readmitted on June 23, 1955. She had been confined to bed with anorexia, nausea, and vomiting for one week. She had no fever, appeared tired, weak, and chronically ill, but was alert and cooperative. The pulse rate was 100 per minute; the blood pressure was 145/75 mm. Hg. The arterial walls were markedly thickened, and the abnormalities in the bones of the hands, toes, and maxillae were unchanged. Bossing of the frontal bones was very prominent. The parathyroids were not palpable. The heart was slightly enlarged to the left, and a soft blowing systolic murmur was heard over the precordium. No abnormality was found on examination of the lungs and abdomen. The hematocrit was 26%, and she was given 1,500 ml. of whole blood, with some improvement in her condition. There was proteinuria, 4+; but the tests for glucose and acetone were persistently negative. In the urinary sediment there were a few erythrocytes, leukocytes, hyaline and granular casts, and oval fat bodies. She excreted 308 mg. of calcium per 24 hours but was not on a restricted calcium intake at this time. In the hospital the dietary regimen was unchanged. At home her condition continued to deteriorate.

Final Admission to Hospital.—On Sept. 1 the patient was readmitted because she had become extremely weak and lethargic and in the preceding week had been vomiting three to four times daily. She had continued to drink well, but the urine volume was decreasing, and she complained of burning on urination. For a few days she had had a throbbing pain in the right fifth finger, and her face had recently become puffy.

In addition to the abnormalities already described she was extremely ill, haggard, pale, and lethargic. The recession of hair, the frontal bossing, and the bilateral maxillary cysts were more pronounced. There was a hot, red, tender cystic swelling of the right fifth finger, and the sternoclavicular junctions were unduly prominent. Uremic frost was noted on the skin of the face. The blood pressure was 150/115 mm. Hg.; the pulse was 96 per minute. The heart was slightly enlarged, and a systolic murmur was heard over the precordium; the liver was slightly enlarged and tender. Details of the biochemical data appear in Table 1. She became steadily worse. The blood pressure rose to 250/130 mm. Hg; she had several epileptiform convulsions, became stuporous or semicomatose, and died on Sept. 30.

Postmortem Examination.—Necropsy was performed two and one-half hours after death. The emaciated body weighed 37 kg. and measured 150 cm. Sexual development was normal. The skin was pale, and there was considerable recession of hair from the scalp.

Kidneys.—The right kidney weighed 80 gm.; the left, 70 gm. The capsules stripped easily, leaving granular surfaces studded with cysts measuring from 0.5 to 1.5 cm. across (Fig. 5). On section some of these cysts contained clear fluid, others gray putty-like material. Overlying the cystic areas the cortex was about 0.2 cm. thick; between these areas it was up to 0.6 cm. thick. There were areas of yellowish discoloration in the cortex measuring up to 0.2 cm. The renal pelves were normal in size and lined by gray granular mucosa. The ureters

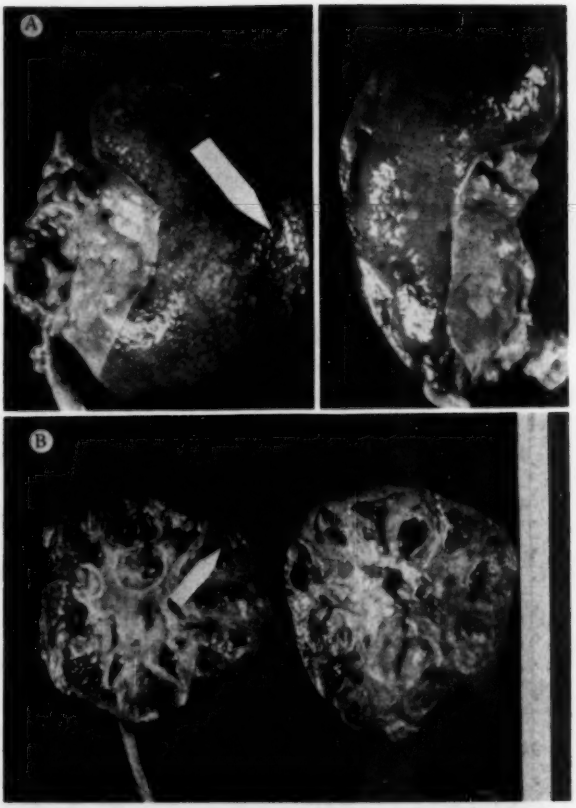

Fig. 5.—Gross appearance of the kidneys, which weighed 70 and 80 gm. Note the granular surface studded with small cysts. *A*, the arrow points to a small cortical abscess. *B*, on cut section marked atrophy of the cortex is seen, and there are many cysts throughout both kidneys. The arrow points to a small cortical abscess.

were patent throughout, and there was no obstruction in the urethra.

On microscopic examination (Fig. 6) the number of glomeruli was greatly diminished and most of the recognizable glomeruli were hyalinized. The Bowman's capsules of the few relatively normal glomerular tufts were thickened by fibrous tissue. In most areas the tubules were replaced by dense sheets of fibrous tissue in which many lymphocytes and plasma cells were seen; in other areas there were small acute abscesses. Elsewhere the tubules were distended and were lined by atrophic epithelium, and many contained casts of bright eosinophilic material.

In the medulla some tubules were filled with polymorphonuclear leukocytes. Flecks of calcium were seen in and around some of the tubules. There was fibrous thickening of the walls of the arteries and arterioles. Large cysts were found throughout both kidneys. Most were lined by cuboidal epithelium; a few, by fibrous tissue. They were surrounded by dense fibrous connective tissue. The pelvic epithelium had been desquamated, and many polymorphonuclear leukocytes were found in these areas and surrounding the pyramids.

Parathyroids.—All four parathyroids were enlarged (Fig. 7). The upper right parathyroid weighed 0.71 gm.; the lower right, 0.26 gm. The left parathyroids were not weighed but were of comparable size. Microscopically two types of cells were observed. Most had well-defined cell membranes and lightly staining vacuolated cytoplasm; their nuclei were uniform, and the chromatin was distributed in dense stipples. These chief cells were arranged in sheets and nests (Fig. 8). There were a few scattered groups of oxyphil

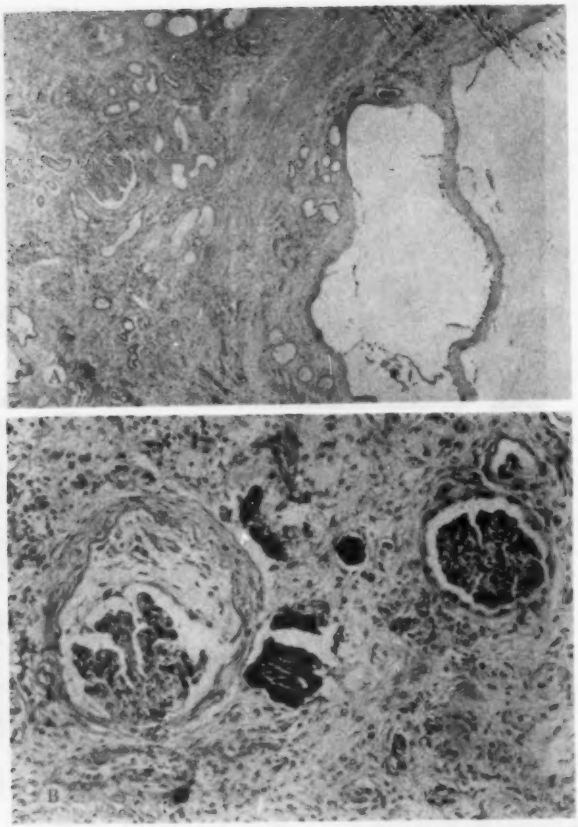

Fig. 6.—The kidney microscopic appearance; *A*, a large cyst lined by small flat cells and fibrous tissue. Note the well-marked interstitial fibrosis. The surviving tubules are distended and lined by a flattened atrophic epithelium. Hematoxylin and eosin; reduced 40% from mag. × 55. *B*, the severe tubular atrophy and marked interstitial fibrosis are well seen. Note the periglomerular fibrosis and the interstitial calcium deposits. Hematoxylin and eosin; reduced 40% from mag. × 150.

Fig. 7.—Parathyroid glands. The enlarged right lower, left upper, and lower parathyroid glands seen in situ.

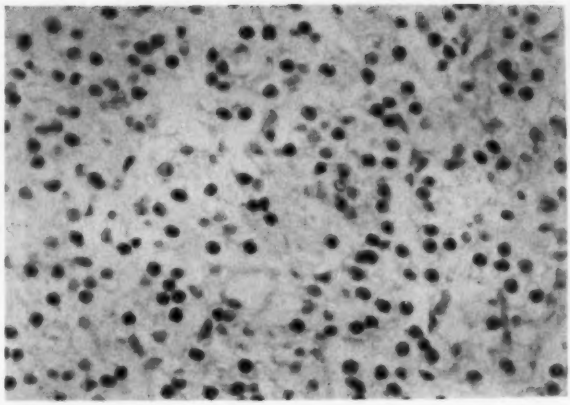

Fig. 8. — Parathyroid glands. The cells are uniform throughout this field. There are large clear vacuoles in their cytoplasm. Hematoxylin and eosin; reduced 35% from mag. × 800.

cells, which were larger and had more eosinophilic cytoplasm; their nuclei were small and pyknotic. No adipose tissue was found in the parathyroids.

Bones.—The frontal bones were prominent and bossed. There were bilateral maxillary enlargements; the larger was on the right, measured 4×3 cm., and was raised 2 cm. The calvarium was thickened, measuring 1.8 to 2.0 cm. It was soft and pliable and cut easily with a knife. The distal phalanges of the fingers and toes were bulbous. The costochondral junctions were enlarged and measured up to 1.5 cm. across. The remaining bones were soft and cut easily.

The right second toe was studied microscopically. The terminal phalanx was surrounded by dense fibrous tissue. The cortical bone was destroyed, and the marrow spaces at its distal end were occupied by loosely arranged fibrous tissue. Replacing the cortical bone were irregular bone spicules lined by a thin layer of osteoid. Osteoclasts were seen in Howship's lacunae and scattered in the marrow spaces (Fig. 9). Similar changes of less degree were seen in the middle and proximal phalanges. On the flexor surface of the proximal phalanx there was an area of loosely arranged fibrous tissue surrounding the tendon sheaths; many small flecks of calcium were deposited in it.

There were bulbous thickenings of the costal cartilages. The cartilage was arranged in large irregular masses separated by fibrous tissue and, in places, surrounding areas of cancellous bone. There was much fibrosis of the marrow spaces of the ribs, in which the abnormalities were similar to those seen in the phalanges. The marrow spaces of the skull were filled with loosely arranged fibrous tissue. The bone was arranged in irregular spicules and was lined by thin osteoid seams and osteoblasts; only a few osteoclasts were seen.

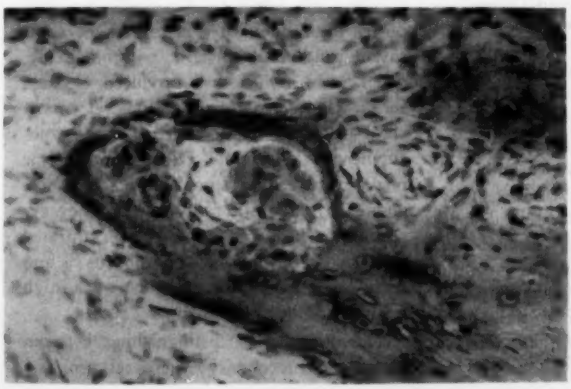

Fig. 9.—Bone from the distal phalanx of the right second toe. The marrow space is almost completely replaced by fibrous tissue. In the center of the trabecula there are numerous osteoclasts. Hematoxylin and eosin; reduced 40% from mag. × 500.

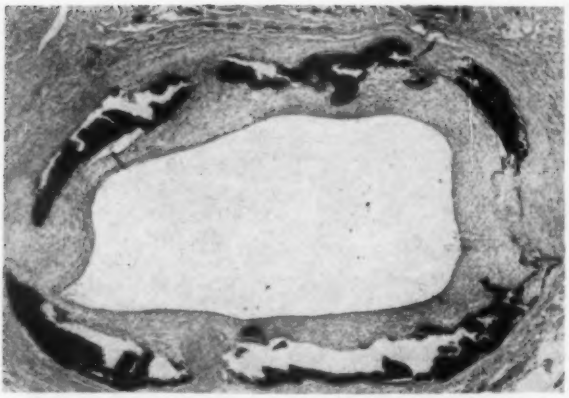

Fig. 10.—Artery of medium size. Note the large deposits of calcium in the media. Overlying these deposits there is fibrosis of the intima. Hematoxylin and eosin; reduced 40% from mag. × 55.

Similar alterations were seen in the vertebral bodies; however, the osteoclasts were more prominent and the marrow spaces contained much hematopoietic tissue. The trabeculae were lined by fibrous tissue, and in many places fibrous tissue strands appeared to have replaced resorbed trabeculae. However, the trabecular pattern was denser in the vertebral bodies than elsewhere.

Arteries.—The large arteries were all considerably thickened, slightly tortuous, and firm. Large deposits of calcium were arranged in circular fashion in the media, and there was fibrous thickening of the overlying intima (Fig. 10).

No abnormality was found in the remainder of the postmortem examination save for slight enlargement of the heart, bronchopneumonia in the right lower lobe, and uremic colitis with ulceration.

Postmortem Diagnoses.—Small congenital polycystic kidneys; severe, acute, and chronic pyelonephritis; uremia with uremic colitis; hyperplasia of the parathyroid glands; generalized osteitis fibrosa cystica; left ventricular hypertrophy, and terminal bronchopneumonia.

Comment

Differential Diagnosis of Hyperparathyroidism in This Patient.—When first seen the patient presented many features of hyperparathyroidism. The whole skeleton was decalcified; the characteristic ground-glass appearance was noted on the x-rays of the skull, and the lamina dura was completely absent. Pseudocystic changes were noted in the left fourth metacarpal bone. Subperiosteal resorption was seen in many bones, an appearance which Dent and Hodson [11] and Pugh [12] considered to be diagnostic of hyperparathyroidism. The clinical and radiological changes in the terminal phalanges were unusual. The fingers resembled clubs, the deformity being the result of the very marked resorption of bone and consequent shortening of the terminal phalanges (Figs. 1 and 2). This abnormality, which may occur in primary hyperparathyroidism, has been reported in cases of secondary hyperparathyrodism by Herbert, Miller, and Richardson [13] and by Wigley and Hunter.[14] Dent and Hodson have pointed out that the bone changes of primary and secondary hyperparathyroidism are indistinguishable radiologically.[11]

Metastatic calcification has not been reported in uncomplicated primary hyperparathyroidism but may occur late in the disease, when renal failure has produced elevated serum phosphorus levels. However, metastatic calcification in periarticular and subcutaneous tissues and calcification of the media of arteries are not uncommon in secondary hyperparathyroidism.[15-17] They occur only when the serum is oversaturated with both calcium and phosphorus [18] and therefore only in the presence of a high serum phosphorus level.[18]

The difficulty in distinguishing between primary and secondary hyperparathyroidism

in this patient was complicated further by the knowledge that secondary hyperparathyroidism may develop as a result of the renal insufficiency of primary hyperparathyroidism.[11,15,19] Severe renal involvement was an outstanding feature of her illness. It was apparent that the diagnosis was either chronic renal disease with secondary hyperparathyroidism or parathyroid adenoma or hyperplasia with severe secondary renal involvement. The history of prolonged asthenia and of polyuria and polydipsia may occur in either condition. Even the history of "pyelitis" at the age of 10 years could not be accepted as conclusive evidence against primary hyperparathyroidism, for Albright and his colleagues have observed that renal symptoms occur before skeletal abnormalities in many patients with primary hyperparathyroidism.[20]

In the early stages the two disorders may be distinguished from each other by the characteristic changes in the serum calcium and phosphorus levels. When impairment of renal function is severe, as in this patient, these estimations are of little differential diagnostic value unless the serum calcium level is greatly elevated. Increased levels of alkaline phosphatase measure only the extent, severity, and activity of bone involvement due to overactivity of the parathyroids, and tests of renal function do not indicate the cause of the impairment of function.

The renal lesion in hyperparathyroidism was described by Albright and his colleagues [21] and was reviewed by Anderson [22] and by Morgan and Maclagan.[23] The lesion is predominantly in the interstitial tissue of the kidney which is infiltrated by chronic inflammatory cells and by fibrous connective tissue. Calcium is deposited in, or adjacent to and around, the tubular basement membrane. Tubular and intraluminar calcium deposits occur but are less prominent, particularly in the late stages. The tubules may be dilated and are frequently lined by a flattened epithelium. There are no proliferative changes in the glomeruli, which are often completely or partially fibrosed. Vascular changes are usually slight. The development of calculi with obstruction and consequent infection may, however, modify the histological picture.

The morphological differentiation of this lesion from that of pyelonephritis may be difficult. Nonetheless, in this case, renal biopsy, which has proved to be of value in the differential diagnosis of many diseases affecting the kidney,[24] gave invaluable information. The changes in her kidney were those of far-advanced pyelonephritis, and there was little to favor a diagnosis of primary hyperparathyroidism. There was no peritubular or intratubular calcification. The few scattered deposits of calcium seen in the interstitial tissue may be found in any chronic renal disease. More strongly than any other investigation the renal biopsy pointed to the kidney as the site of the primary disease. It was therefore decided not to explore the neck for a parathyroid adenoma. The postmortem findings of polycystic kidneys with severe chronic pyelonephritis and of four enlarged parathyroid glands with principal-cell hyperplasia were later to justify this clinical decision.

Incidence and Clinicopathologic Features of Renal Disease with Secondary Hyperparathyroidism.—Our interest in the patient reported above prompted a search of the literature for reports of similar cases. Twenty-five were found (Table 2). A few cases diagnosed by other authors have been excluded from this review because they did not meet all three of the criteria given in the introduction to this paper. Excluded also from the review are the cases reported by Gilmour.[42] He found microscopic evidence of osteitis fibrosa in 20 cases of chronic renal insufficiency; in 15 the parathyroid glands were greatly hypertrophied. In five patients Gilmour noted osteitis fibrosa without considerable parathyroid gland enlargement. Unfortunately the terminology used in his monograph is so complicated that we were unable to evaluate his data adequately.

Although from the literature we were able to accept but 25 cases for inclusion in this discussion, the reports of Berner,[2] Gilmour,[42] and Follis [4,43] suggest that the asso-

TABLE 2.—*Cases of Renal Disease with*

Author	Age	Sex	Duration of Renal Disease, Yr.	Serum Chemistry: Calcium, Mg/100 Ml.	Phosphorus, Mg/100 Ml.	Alkaline Phosphatase, Units	CO_2, mM/L.	BUN, Mg/100 Ml.	N. P. N. Mg/100 Ml.	Blood Pressure, Mm. Hg
Langmead & Orr [33] (1933)	20	M	>6					62–166		126/98 190/78
Smyth & Goldman [34] (1934)	14	M	Unknown	10.5–11.9	10.9–16.0	11.7	22		80–333	110/56
Shelling & Remsen [37] (1935)	17	M	Unknown	9.3–9.9	7.7–10.5	22.1	21		153–364	110/72
Castleman & Mallory [35] (1935) (Case 23A)	25	F	Lifelong polyuria	8.0	9.0				150	156/78
Kluge [36] (1937) (Case 4)	19	F	713	8.4 †	18.0 †				297 †	140/90
Albright et al. [38] (1937)	45	M	23	8.2	9.8	9.4(B)	17		120	165/90
Pons & Pappenheimer [40] (1937)	33	M	>9					63–90	134–200	132/92
Price & Davie [41] (1937)	14	M	>12	13.6–12.5	6.5–5.0	89.6		149		120/75
Howard [42] (1938)	16	M	Unknown	10.5–6.9 –10.6	6.0–11.3		14		109–172	110/40
Schellack [43] (1939)	2	F	2	7.2–9.7	3.5–6.0				66–154	
Herbert, et al. [44] (1941)	40	F	>4	11.7	7.8	32.4 (JK)		140		180/110
Gall & Bennett [45] (1942)	13	M	>1½	5.9 †	17.4 †		7 †	200 †	378 †	150/80
Smyth & Yearell [46] (1942)	21	F	20	5.9‡–11.0	3.5–10.4	6.0–39.0 (JK)	10-32 32		60–190	
Snapper [1] (1949) (Case 1)	18	?	15	10.0–10.2	8.0–10.5					
Snapper [1] (1949) (Case 2)	14	F	7	8.3–11.5 –12.8	8.0–10.0 –4.8	63 (KA)	"Relatively normal"	27–100		172/110
Dreskin & Fox [47] (1950) Pollak et al. (Case 5)	27	M	21	10.4–4.2	8.7–15.2	6.7–22.0 (B)	15	81–150	69–288	116/44

ciation of osteitis fibrosa and parathyroid hyperplasia with chronic renal disease is not uncommon. An attempt was made, therefore, to assess the frequency of hyperparathyroidism in patients ill with renal disease. The case records of patients dying between January, 1944, and December, 1955, of chronic renal disease with uremia at the University of Illinois Hospitals were reviewed. Autopsies were done on 91 such patients, in 17 of whom there was pathological evidence of chronic renal disease, osteitis fibrosa, and enlargement of the parathyroid glands. In five patients, including the case reported in this paper, the pathological changes in the bones were of considerable severity, and a summary of the clinical and pathological changes in these patients is shown in Table 2. One of the five has been reported previously and in

Secondary Hyperparathyroidism from the Literature

Clinical Evidence of Bone Disease	Pathology			
	Bones	Metastatic Calcification	Parathyroids	Kidneys
Renal rickets; osteoporosis; ? Osteitis fibrosa	Osteitis fibrosa	Not recorded	4 Enlarged; probably chief-cell hyperplasia	Total weight 100 gm.; interstitial nephritis
Renal rickets; probable osteitis fibrosa; no cysts; clubbed fingers	Osteitis fibrosa	Soft tissues, arteries, kidneys	5 Enlarged; chief-cell hyperplasia	Weight 35 gm., 35 gm.; Hydroureter and hydronephrosis; calcification
Demineralization; deformities; ? osteitis fibrosa; no cysts	Osteitis fibrosa	Arteries, subcutaneous tissue	4 Enlarged; chief-cell hyperplasia	Weight 65 gm., 70 gm.; hydroureter, hydronephrosis; no obstruction; chronic pyelonephritis; acute pyonephrosis
Cysts on x-rays	Osteitis fibrosa	Arteries, subcutaneous tissue	3 Enlarged; chief-cell hyperplasia	Severe chronic pyelonephritis
Spontaneous fracture; rickets; dwarfism	Osteitis fibrosa of skull; ? rickets	Arteries	2 Greatly enlarged; 2 small; cells normal	40 gm. total weight; severe chronic pyelonephritis with gross parenchymal fibrosis
Decalcification	Osteitis fibrosa	Arteries; periarticular, subcutaneous tissues	All large (weight 11 gm.); chief cell hyperplasia	85 gm. total weight; chronic glomerulonephritis
Thought to have Cushing's syndrome	Osteitis fibrosa	Arteries, kidneys	4 Enlarged (3.46 gm.); chief-cell hyperplasia	Weight 115 gm., 105 gm.; cysts throughout; probably pyelonephritis
Rickets; osteitis fibrosa; no cysts	Osteitis fibrosa + ? rickets	Kidneys	4 Much enlarged, chief-cell hyperplasia	Very small; many small cysts; pyelonephritis
Rickets	Osteitis fibrosa + ? rickets	Vessels, kidneys	3 Much enlarged, chief-cell hyperplasia	Weight 36 gm., 22 gm.; probable pyelonephritis
Spontaneous fracture	Osteitis fibrosa; no rickets	Heart muscle	4 Enlarged (0.47 gm.); chief-cell hyperplasia; islands of oxyphils	Small; interstitial nephritis with severe interstitial fibrosis
Absorption of portion of terminal phalanges of hands	Osteitis fibrosa, cysts	Arteries, soft tissue	4 Enlarged (5.21 gm.); chief cells & many oxyphils	Weight 22 gm., 27 gm.; hypoplasia or glomerulonephritis
Legg-Perthe disease; increased radiolucency of long bones	Osteitis fibrosa	Not recorded	4 Enlarged; chief & transitional cells; few oxyphils	Agenesis right kidney; left weighed 19.5 gm.; chronic pyelonephritis, severe
Ground-glass skull, no rickets	Osteitis fibrosa	Arteries, lungs, kidneys	3 Enlarged chief-cell hyperplasia; groups of oxyphils	Weight 32 gm., 42 gm.; hydroureter, hydronephrosis; chronic pyelonephritis
	Osteitis fibrosa	Arteries, lungs, heart, subcutaneous tissue	4 Enlarged; chief-cell hyperplasia	Chronic glomerulonephritis
Generalised decalcification; irregular epiphyseal disks	Osteitis fibrosa	Subcutaneous tissue	4 Enlarged (1.06 gm.); chief-cell hyperplasia	Chronic glomerulonephritis
Mottling of calvarium; cyst in metacarpal	Osteitis fibrosa cystica	Arteries, soft tissue	1 Large gland removed at operation; several enlarged post mortem, chief-cell hyperplasia	Weight 120 gm., 80 gm.; hydroureter, hydronephrosis; chronic pyelonephritis

some detail by Dreskin and Fox.[36] In 12 patients the bony changes were less severe, the osteitis fibrosa being classified as moderate in 3 and as mild in 9. In each case the lesions in the bones were classified and evaluated to indicate the extent of bone resorption, the presence and degree of fibrosis, and the number of osteoclasts. Hyperparathyroidism was diagnosed during life in only two of the five patients classified as having severe lesions and was not diagnosed during life in any of the others.

Details of the renal pathology of our five severe cases and of those culled from the literature are set forth in Table 2. These findings are summarized in Tables 3 and 4, which also give the findings in the 12 cases in our postmortem series with mild or moderate osteitis fibrosa. From Table 3 it is seen that pyelonephritis, either alone or

TABLE 2.—*Cases of Renal Disease with Secondary*

Author	Age	Sex	Duration of Renal Disease, Yr.	Serum Chemistry: Calcium, Mg/100 Ml.	Phosphorus, Mg/100 Ml.	Alkaline Phosphatase, Units*	CO_2, mM/L.	BUN, Mg/100 Ml.	N. P. N. Mg/100 Ml.	Blood Pressure, Mm. Hg
Richards [37] (1951)	44	F	22	10.9–13.3	8.7		14 †	74–170		200/110
Joiner & Thorne [38] (1953) (Case 1)	30	F	22	11.4–11.0	7.4–3.6	21.4 (KA)	18	54–187		160/90
Joiner & Thorne [38] (1953) (Case 2)	33	F	Unknown	9.5–10.0	5.5–8.0	63.0 (KA)	19–14	74–212		140/100
Morgan & Maclagan [39] (1954) (Case 1)	25	M	Unknown	7.8–9.9	5.3–8.8	20–44 (KA)	18–14	83–271		Normal
Morgan & Maclagan [39] (1954) (Case 2)	22	F	>1½	9.1–10.5	6.0–8.3	32–58 (KA)	19–15	93–131		210/130
Crawford et al.[9] (1954)	26	M	>17	6.0–6.9	5.9–8.2	41 (KA)	12.9–26	121–75 –280		152/110
Crawford & La Zerte [40] (1955)	45	F	Unknown	8.8	11.1	13.8(B)	9		122	126/70
Ericson & Svanborg [41] (1956) (Case 1)	27	F	>3	10.0	13–16	7(Buch)	15		100–240	120/80
Clinicopathological conference [42] (1956)	42	F	>10	11.5	17.3	9.3(B)	12.8		347	210/120
Pollak et al. (Case 1)	25	M	>7	10.4	11.7	1.1 (B)	12 †	208–240 †	249–339 †	166/96
Pollak et al. (Case 2)	22	M	720	8.7	14.0		23–15	161–210	157–273	172/116
Pollak et al. (Case 3)	16	F	Unknown	5.0 †	10.8–12.3 †	4.3(B)	14–23 †	220–250	252–303 †	125/80
Pollak et al. (Case 4, this patient)	18	F	>8 ?18	9.9–8.4 †	9.4–6.7 –8.3	9.4–16.4 (B)	19–25–14	117–79 –142	143–102 –284	160/110– 250/130

* B indicates Bodansky units; JK, Jenner-Kay units; KA, King-Armstrong units.

† Values obtained just before death or on blood obtained post mortem.

‡ Value of 5.9 obtained 10 years before death; all subsequent calcium determinations were within the normal range.

in combination with other renal diseases, occurred in 24 of the 29 severe cases and in 8 of the 12 cases of less severity. Joiner and Thorne have previously drawn attention to the high incidence of pyelonephritis in this group of patients.[38] Congenital lesions were found in four or five cases; all had superimposed pyelonephritis. By contrast the incidence of uncomplicated glomerulonephritis was low. In the majority, the severity of the interstitial fibrosis was striking, irrespective of the primary pathology. In the severe cases the weights of the kidneys were low (Table 4). In 12, the combined weight of the two kidneys was less than 120 gm.; only in 3 instances did it exceed 180 gm. In the milder cases the kidneys were larger. Nonetheless, there was no

Hyperparathyroidism from the Literature—Continued.

Clinical Evidence of Bone Disease	Pathology			
	Bones	Metastatic Calcification	Parathyroids	Kidneys
Ground-glass skull	Osteitis fibrosa, no rickets	Arteries, aorta, heart, lungs	4 Enlarged; chief, transitional; small number of oxyphils	Interstitial nephritis
Osteoporosis	Decalcification & replacement fibrosis	Arteries, soft tissues	Enlarged; histologically indistinguishable from normal	Weight 90 gm., 105 gm.; pyelonephritis
Generalized decalcification	Fibrous replacement of bone; osteoblasts & osteoclasts	Arteries	Enlarged; diffuse hyperplasia of uniform histology	Weight 15 gm., 20 gm.; pyelonephritis
Bone cysts	Advanced osteitis fibrosa	Arteries	2 Enlarged (1.2 gm.); chief-cell hyperplasia	Total weight 85 gm.; chronic pyelonephritis
Slight clubbing of fingers	Generalized osteitis fibrosa	Arteries, subcutaneous tissue	4 Enlarged (2 weighed 2.44 gm.); chief-cell hyperplasia; 1 oxyphil nodule	Weight 85 gm., 85 gm.; chronic pyelonephritis
Generalized rarefaction; sclerosis of vertebral bodies; bone resorption in areas; absent lamina dura	Generalized osteitis fibrosa; excess lamellar bone formation in vertebrae	Not recorded	3 Enlarged (1.5 gm.); chief-cell hyperplasia with few oxyphils	Infected hydronephrosis; gross parenchymal fibrosis; chronic cystitis; retention of urine due to neurological abnormality
Decreased density of bone; ground-glass skull	Resorption, osteoclasts, osteoblasts; fibrosis; osteitis fibrosa	Heart	Total weight 3.8 gm.; numerous chief cells & oxyphils	Weight 46 gm., 47 gm.; chronic pyelonephritis
Osteoporosis; decalcification	Renal osteodystrophy	Kidneys, lungs, skin, muscle	4 Enlarged (weight 8 gm.); hyperplasia	Total weight 110 gm.; chronic pyelonephritis
Osteitis fibrosa cystica	Generalized severe osteitis fibrosa	Arteries, kidneys, lungs, stomach	3 Enlarged (1.5 gm.); nodules of chief cells & oxyphils	Total weight 125 gm.; chronic glomerulonephritis, plus acute & chronic pyelonephritis
Ground-glass skull; generalized rarefaction; cysts in clavicles	Osteitis fibrosa; bone absorption 3+; osteoclasts 3+; fibrosis 2+; osteoid 1+	Heart, lungs, skin, adrenals, pituitary, kidney	All enlarged; largest 1.2 cm.; chief cells & few oxyphils	Weight 85 gm., 90 gm.; chronic pyelonephritis
Not diagnosed	Osteitis fibrosa; bone absorption 3+; osteoclasts 3+; fibrosis 2+; osteoid 1+	Kidney	3 Enlarged; largest 1.4 cm.; chief cells & few oxyphils	Weight 55 gm., 105 gm.; chronic glomerulonephritis with superimposed pyelonephritis
Not diagnosed	Osteitis fibrosa; bone absorption 2+; osteoclasts 2+; fibrosis 2+; osteoid 1+	Not recorded	2 Enlarged; 5×4×4 mm.; chief-cell hyperplasia	Weight 70 gm., 90 gm.; chronic pyelonephritis
Ground-glass skull; cysts; subperiosteal bone resorption; absent lamina dura	Osteitis fibrosis cystica (see text)	Arteries, soft tissues, kidneys	4 Enlarged; 2 weighed 0.97 gm.; (see text)	Weight 80 gm., 70 gm.; small polycystic; chronic & acute pyelonephritis

definite correlation between the size of the kidneys and the severity of the osteitis fibrosa.

Hyperplasia of the chief cells was the most striking feature of the histology of the parathyroid glands. It was found in all 35 cases in which the histology was described; in 16, small islands of oxyphil cells were also observed. An exact correlation could not be made between the size and weight of the parathyroid glands and the severity of the bone lesions. However, in general it appeared that greatly enlarged glands were associated with the more pronounced bone changes. It is pertinent to recall that in spontaneous chronic canine nephritis Platt found a good correlation between the size of the parathyroid glands and the severity of the osteitis fibrosa.[44] However, Berner,[2] Gilmour,[42] and Follis[43] described some cases of severe osteitis fibrosa without significant parathyroid hyperplasia.

TABLE 3.—*Renal Lesions in Forty-One Patients Dying of Renal Disease with Secondary Hyperparathyroidism*

Renal Pathology	Osteitis Fibrosa	
	Severe (29 Cases)	Mild (12 Cases)
Pyelonephritis or interstitial nephritis	14	3
Hydronephrosis with pyelonephritis	4	0
Glomerulonephritis	3	3
Polycystic kidneys with pyelonephritis	3	1
Glomerulonephritis and pyelonephritis	2	3
Agenesis of kidney and pyelonephritis	1	0
Hydronephrosis	1	0
Diabetic nephropathy	0	1
Diabetic nephropathy with pyelonephritis	0	1
?agenesis of kidney ?glomerulonephritis	1	0
Pyelonephritis alone or complicating other renal lesions	24	8
Glomerulonephritis alone or with other renal lesions	5 or 6	6

Ectopic calcification was found in 23 severe cases. Calcification was observed in the arteries in 18, the soft tissues in 13, the kidneys in 9, the heart in 5, and the lungs in 5 cases. In the group of 12 cases with less severe osteitis fibrosa, renal calcification was found in 5 and calcification of the arteries in 2 instances. Herbert, Miller, and Richardson [13] and Reifenstein [45] have pointed out that ectopic calcification is likely to occur when the serum is oversaturated with calcium and phosphorus, namely, when the product Ca×P (both in milligrams per 100 ml.) exceeds 30 to 40. In every patient with ectopic calcification Ca×P was greater than 30; in one case, with slight calcification limited to the kidney, the product was only slightly elevated, to 33. In only two patients in whom ectopic calcification was not demonstrated was Ca×P greater than 30.

TABLE 4.—*Combined Weights of the Two Kidneys in Forty-One Patients Dying with Chronic Renal Disease and Secondary Hyperparathyroidism*

Weight, Gm.	Osteitis Fibrosa	
	Severe (29 Cases)	Mild (12 Cases)
0-60	5	0
61-120	7	2
121-180	7	2
>180	3	6
Not recorded	7	2

Of the 41 patients with hyperparathyroidism secondary to renal disease, the majority were young, 28 dying before the age of 30 years (Table 5). The sex incidence was almost equal (13 males, 15 females) among those with the severe degrees of osteitis fibrosa; there were more males among those with lower degrees of bone involvement. Snapper [3] and Herbert, Miller, and Richardson [13] have observed that the renal disease had usually been of very long duration in patients with hyperparathyroidism. The estimation of the duration of the renal disease from the clinical protocols available was difficult and, of necessity, inaccurate. Nevertheless, renal disease was known to have been present for 10 or more years in 14 of the 22 cases in which an estimate of the duration could be made. Eight of these had had evidence of renal disease for 20 years or more. It seems reasonable to conclude that in many cases secondary osteitis fibrosa develops when renal disease has been manifest over long periods of time and when the kidney damage has progressed gradually.

TABLE 5.—*Age at Death of Forty-One Patients Dying with Chronic Renal Disease and Secondary Hyperparathyroidism*

Age, Yr.	Osteitis Fibrosa	
	Severe (29 Cases)	Mild (12 Cases)
0-10	1	0
11-20	11	2
21-30	10	5
21-40	3	2
>40	4	3

Is Osteitis Fibrosa a Result of Hyperfunction of the Parathyroid Glands?—Although osteitis fibrosa and significant parathyroid hyperplasia occur in patients with chronic renal disease, many have been unwilling to accept the view that the bone changes result from hyperparathyroidism. Increased amounts of circulating parathyroid hormone have not been demonstrated,

but this cannot be accepted as a valid argument at the present time, since reliable chemical or biological assay methods for parathormone in blood do not exist. Albright and his colleagues believed that the low serum calcium level of renal failure led to parathyroid hyperplasia; however, they considered that bone resorption resulted not from excess parathyroid hormone activity but from the metabolic acidosis of renal failure.[20] The following observations indicate that it is unlikely that the acidosis per se is the only cause of osteitis fibrosa.

The osteitis fibrosa of renal disease is histologically identical with that occurring in primary hyperparathyroidism—which is not accompanied by a metabolic acidosis.[7-10] The metabolic acidosis in the 29 patients with severe osteitis fibrosa, discussed in this paper, was not unduly pronounced for a group of patients with severe chronic renal failure.*

It is well known that an increased secretion of parathyroid hormone results in an elevation of the serum calcium level and a decrease of the serum phosphorus level.[45] In most cases of chronic renal failure the serum calcium level is low[46,47] and the phosphorus level elevated. However, in long-standing renal insufficiency with secondary hyperparathyroidism the serum calcium level is said frequently to be normal, increased,[6,48] or only slightly lower than normal.[38] Serum calcium values were available for 34 patients. In only 5 were the values less than 7.0 mg/100 ml., and they were found to be elevated or normal in 20 instances. In all the elevation of the blood urea nitrogen or nonprotein nitrogen levels was marked, and in many it was extreme (Table 2). The levels of serum calcium in these patients were therefore unusually high, considering the degree of azotemia.†

If the serum calcium is low in uncomplicated long-standing renal failure the subsequent development of hyperparathyroidism would tend to raise the serum calcium toward or above normal. This sequence of events probably occurred in the patient reported by Smyth and Yeazell.[35] This patient died at 21 years of age from chronic pyelonephritis and secondary hyperparathyroidism. Ten years earlier the nonprotein nitrogen was 84-129 mg/100 ml. and the serum calcium 5.9 mg/100 ml. Thereafter, despite persisting azotemia and impaired renal function, the serum calcium level increased to between 9.6 and 11.5 mg/100 ml.—a level which was maintained for nine years before she died. Few of these patients have been followed for more than one year, and confirmation of this concept will depend on long-term follow-up of many patients with chronic renal disease.

In the patient reported by Dreskin and Fox[36] the course of events strongly suggested that an excess of circulating parathyroid hormone was responsible for the skeletal abnormalities. This patient had had renal disease for 21 years before he died. He had well-marked osteitis fibrosa cystica, metastatic calcification, a normal serum cal-

* The levels of serum calcium, phosphorus, CO_2-combining power, and blood urea nitrogen from 29 cases of renal failure with secondary hyperparathyroidism and severe osteitis fibrosa (Table 2) were compared with levels from 36 unselected cases of renal failure gleaned from the literature.[43,47,49,50]

	Renal Failure with Hyperparathyroidism	Unselected Group of Patients with Renal Failure	*t*-test
BUN, mg/100 ml.	137±39	130±63	$P>0.5$
P, mg/100 ml.	9.1±3.04	9.6±3.78	$P>0.5$
CO_2-comb. power, mEq/L.	17±3.32	19±3.93	$P>0.5$
Ca, mg/100 ml.	10.1±1.59	7.4±1.25	$P<0.001$

It will be noted that the levels of serum phosphorus, CO_2-combining power, and blood urea nitrogen were comparable in the two groups. The serum calcium level was significantly greater in the group with secondary hyperparathyroidism.

† See previous footnote.

cium level, and a moderately elevated serum phosphorus level. When one greatly enlarged parathyroid gland was removed, the osteitis fibrosa healed, there was absorption of metastatic calcium deposits, the serum calcium fell to a low level, and the serum phosphorus rose. Moderate acidosis persisted unchanged, and the bone lesions healed despite this. These observations strongly suggest that this patient had increased parathyroid hormone secretion from a very hyperplastic gland before operation and that after the operation the secretion of the other three hyperplastic glands was insufficient to modulate the effect of the renal disease on the serum calcium and phosphate levels. In this patient it seems reasonable to attribute to the parathyroid hormone secretion not only the effects on the serum calcium and phosphorus but also the effects on the bones. On the basis of the evidence available at the present time we must conclude that the hyperplastic parathyroid glands found in these patients with chronic renal disease and osteitis fibrosa do in fact secrete an abnormal amount of parathyroid hormone.

Summary

Only 25 well-documented examples of hyperparathyroidism secondary to renal disease were found in the medical literature. Nevertheless, we found evidence of secondary hyperparathyroidism in 17 of 91 consecutive patients dying of chronic renal diseases. Severe bone lesions were observed in 5, lesions of mild to moderate severity, in 12 instances.

The commonest renal lesion was pyelonephritis, either alone or in combination with other lesions. Congenital lesions were also frequently observed. The incidence of uncomplicated glomerulonephritis was comparatively low.

Secondary hyperparathyroidism occurred particularly in the second and third decades of life and frequently in patients with renal disease of very long duration. The serum calcium level was often normal or elevated and was significantly higher than in a comparable group of patients with renal failure who did not have secondary hyperparathyroidism. Ectopic calcification occurred in most patients.

One patient, studied in detail over a period of 11 months, is reported fully. The differential diagnosis between primary renal disease with secondary hyperparathyroidism and parathyroid adenoma with secondary renal disease was difficult but was settled by renal biopsy, which revealed primary renal disease.

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Hypotension as a Complication of Promazine Therapy

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The use of promazine as a tranquilizing agent in the treatment of a variety of disease states has achieved widespread currency. Recent reports have appeared concerning its efficacy in the management of patients with both acute and chronic mental disturbances,[1,2] including alcoholism[3,4] and delerium tremens,[5] as well as its use as a predelivery sedative.[6]

A prime factor leading to the extensive use of this drug has been the generally accepted belief that removal of the chloride ion from chlorpromazine leads to diminished toxicity without loss of therapeutic potency. It has been frequently stated that use of the drug is not attended by serious side-effects.[1-6] However, isolated reports of toxic complications, including agranulocytosis,[7-9] convulsions, and dermatitis,[10] have appeared. Another complication, marked hypotension, which is more properly considered an anticipated pharmacologic effect, has been observed[3,10] but is said to be "slight," [6] "moderate," [1] and, in fact, "not encountered." [5] Though mention is made of a death following vasomotor collapse after use of promazine,[11] hypotension is usually considered as a relatively benign side-effect of the use of this drug.[12]

Serious and even fatal hypotensive reactions have recently been observed at this institution following the administration of promazine. While lethal vascular collapse could not be unequivocally attributed to promazine, inasmuch as the patients were suffering from illnesses in themselves very profound, nevertheless the fact that irreversible collapse occurred immediately after the administration of the drug emphasizes the harmful potentialities in susceptible persons.

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Report of Cases

Cases 1 through 3 represent fatalities encountered after promazine administration. Cases 4 through 7 represent nonfatal hypotensive episodes.

CASE 1.—This 53-year-old woman, a heavy drinker with previously demonstrated Laennec's cirrhosis, was admitted about six days after the onset of marked persistent bleeding from the right upper gum margin. Until then, she had been doing well despite heavy drinking. She became progressively weaker and more lethargic, and she was semicomatose when first seen. She was icteric, with brisk oozing from the gum margin, but little else was noted on the examination other than her mental confusion. B. P. was 60/30; pulse, 100; respirations, 16; temperature, 99 F, and Hgb., 5.0 gm. %. After rapid infusion of 1,000 cc. of 5% dextrose in lactated Ringer's injection and of 500 cc. of whole blood, the blood pressure rose to 90/50 and the patient became much more responsive. Her blood pressure remained between 70/40 and 90/62 throughout the night, and at 8:30 a. m. she was much the same but had a rather coarse tremor. Promazine, 75 mg., was given intramuscularly at 9:30 a. m. At 10 a. m., while being reexamined, she suddenly appeared critically ill, with agonal respiratory movements. B. P. was 0/0; pulse, 40 and then 120. A brief return of the heart rate followed intracardiac injection of 50% dextrose in H_2O and 10% calcium gluconate, but she quickly died. Additional laboratory data obtained just before death revealed Hgb., 7.0 gm. %; serum Na, 138 mEq.; serum K, 4.5 mEq. per liter; B. U. N., 16 mg. %; CO_2-combining power, 15 mEq. per liter; Cl, 91 mEq. per liter; protein, 5.5 gm. %, with A/G, 2.7/2.8, and total serum bilirubin, 8.6 mg. %. No fasting blood sugar value was obtained. Postmortem examination revealed marked portal cirrhosis, with extensive fatty metamorphosis, moderate fibrocongestive splenomegaly, and acute passive hyperemia and edema of the lungs.

CASE 2.—This 33-year-old woman, also a chronic alcoholic, began vomiting near the end of a prolonged alcoholic debauch about seven days before admission. She had noted scleral icterus about three

days thereafter and came to the emergency room after persistence of these symptoms. When first seen, she was very apprehensive, with B. P., 160/110; pulse, 110; respirations, 32; definite scleral icterus, and a questionably palpable liver. She was given promazine (Sparine), 25 mg. intramuscularly at 3 p. m. and 50 mg. intramuscularly at 3:45 p. m. Two hours after administration of the last dose she was found to be semicomatose, with an unobtainable blood pressure. After rapid infusion of 5% dextrose in water and inhalation of oxygen the blood pressure rose to 48/0, but she died about three minutes thereafter. Autopsy revealed severe fatty metamorphosis of the liver, which weighed 6,000 gm., and congestion of the viscera.

Case 3.—The patient, a 66-year-old man with rather severe pulmonary emphysema, was found to have an epidermoid carcinoma of the urinary bladder as cause for recurrent hematuria noted for three months. Bilateral ureterosigmoidostomy was performed, but postoperative peritonitis with wound dehiscence occurred. After a colostomy and wound drainage, he improved temporarily. However, after two episodes of heavy leakage of blood from the lower wound margin, he began to feel weak, apprehensive, and nervous, with a fall in hemoglobin from 11.8 to 9.8 gm. %. On the day before death he had a brief hypotensive episode, with fall in blood pressure from 130/85 to 80/40, with prompt response after infusion of salt solution and whole blood. At 7:20 p. m. on Jan. 14, 1957, he complained of increasing nervousness and apprehension and was given promazine, 50 mg. intramuscularly, at which time the blood pressure was 120/80. One hour later blood pressure was found to be 40/20 and then 30/0. After institution of norepinephrine (levarterenol) drip, the blood pressure rose to 65/30, but he died at 11:05 p. m. No postmortem examination was performed.

Case 4.—A frequent visitor to the emergency room, this 35-year-old woman was seen again having tremulousness and agitation after an alcoholic debauch. She was given promazine, 50 mg. intramuscularly, and referred to jail for "sobering-up." While leaving the hospital about 10 minutes after the injection, she fell to the floor and was found to have a blood pressure of 40/20, with marked pallor. Placing her in the Trendelenburg position had no effect, and an infusion of saline with 4 mg. of norepinephrine added was begun, with gradual return of the blood pressure over the next six hours.

Case 5.—This 20-year-old hospital technician was given, by error, a 200 mg. tablet of promazine for nausea associated with a mild gastroenteritis. Upon returning home about one hour after ingestion of the tablet, she fainted; she was found to have a blood pressure of 70/40. She was simply kept in bed and some four hours later was able to sit up, without a fall in pressure from the usual 120/75.

Case 6.—Having also been given a 200 mg. promazine tablet by error, this 44-year-old hospital kitchen helper became weak and dizzy, with fall in pressure from 140/70 to 90/50, thirty minutes thereafter. Return of vasomotor tone followed a four-hour period of recumbency.

Case 7.—This 78-year-old man, a diabetic with coronary and generalized arteriosclerosis, had previously experienced weakness, dizziness, and occasional fainting upon sudden assumption of the upright position. Orthostatic hypotension, with fall in pressure from 125/65 to 80/50, had been demonstrated. Recurrent abdominal pain with anorexia, nausea, and vomiting was investigated, with demonstration of a gastric ulcer. He was given promazine, 50 mg. intramuscularly, for nausea, and there was an occurrence of marked lethargy and weakness within 20 minutes, at which time his blood pressure in the supine position was 80/40. He was kept in the Trendelenburg position and given an infusion of 5% dextrose in water, with a gradual rise in blood pressure and a return of his normal sensorium over the next six hours.

Comment

These case reports should not be taken as evidence against the use of promazine or other phenothiazine derivatives. The many clinical reports on their use as tranquilizers, antiemetic agents, potentiators of analgesic drugs, and sedatives for alcoholics and addicts undergoing drug withdrawal attest to their widespread efficacy. However, the occurrence of seven hypotensive episodes at this hospital in a short period of time after the use of promazine has prompted a review of previous pharmacological and clinical reports. No published pharmacologic studies on promazine could be found. Therefore, it seems reasonable to examine the toxic potentiality of chlorpromazine, which has been subjected to extensive scrutiny, in order to shed some light on the deleterious effects of promazine.

Experimental studies done by Courvoisier, Moyer, Foster, Bourgeois-Gavardin, and Spurr and their associates [13-17] reveal a definite direct peripheral vasodilatation as well as a probable central inhibitory action on the vasomotor center in both animals and man given chlorpromazine. A large number of

clinical studies have shown that parenteral administration of even moderate doses of chlorpromazine is almost invariably followed by orthostatic hypotension, the extent of which is extremely variable and unpredictable but always severer with the initial injection.[18-26] Only a few reports have appeared concerning this side-effect with promazine,[1-3,10] but, as pointed out, "In view of their close structural relationship it is possible that any of the untoward reactions attributed to chlorpromazine could occur after promazine therapy."[12] This has been borne out with all complications other than jaundice secondary to intrahepatic biliary tract obstruction. In this regard, however, one case of recurrence of hepatic dysfunction in a patient given promazine after recovery from two episodes of jaundice following chlorpromazine[27] is of interest.

In regard to the hypotensive effects of these agents, three further points are noteworthy. First, virtually all investigators have made mention of the resistance of the hypotension produced by these drugs to pressor agents, leading to their designation as "adrenergic blocking agents." Large amounts of norepinephrine are usually needed to overcome serious hypotension. This blocking action was recently demonstrated in a patient who was being maintained on a norepinephrine (levarterenol) infusion containing 20 mg. in 1,000 cc. of solution after a platelet transfusion contaminated with Gram-negative organisms. His blood pressure was being kept around 110/70 by a moderate rate of infusion. He was given chlorpromazine, 25 mg. intravenously, with an immediate fall in blood pressure to 40/0. Increase in the rate of infusion and norepinephrine dosage to 64 mg. per liter was thereafter necessary to maintain the blood pressure around 100/70.

Second, the increased sensitivity to these drugs of patients with hepatic disease has been previously noted.[14,28,29] This might be anticipated from the studies revealing a significant excretion of chlorpromazine in the bile with only negligible urinary excretion, as well as its rapid metabolism by rabbit-liver homogenates.[30] This increased sensitivity is emphasized by the first two case reports, wherein the patients were found to have extensive fatty metamorphosis of the liver as the only important pathological finding, and by Case 4, where cirrhosis is probable. It seems plausible to implicate decreased hepatic excretion and breakdown of promazine as a causative factor in the severe hypotension that occurred soon after its administration in doses which are usually not deleterious.

Third, the marked variability in the occurrence and severity of hypotension is perhaps partially explicable by yet another variable, the patient's underlying sympathetic nervous system tone.[16] It is to be anticipated that patients in borderline peripheral vascular collapse with maximal sympathetic stimulation, as Cases 1 and 3, must surely be more susceptible to any blockage of autonomic activity. Exaggerated hypotension following the use of chlorpromazine has been noted following minimal blood loss[23,31] or when sympathetic responsiveness is already altered by spinal, epidural, or celiac plexus block.[26]

Cases 1 and 3 had previously experienced peripheral vascular collapse secondary to marked blood loss; the blood pressure had responded to administration of blood and saline. However, their status remained precarious, and promazine was administered for relief of symptoms which themselves may well have been early manifestations of impending collapse. Even a mild inhibition of a sympathetic nervous system which is maximally stimulated to maintain a compromised circulation might well have led to an irreversible state of collapse. In Case 7, orthostatic hypotension had been observed for many years. Altered sympathetic responsiveness, which may be a feature of this condition, could well explain the occurrence of peripheral collapse after promazine administration.

On the other hand, pretreatment with chlorpromazine has been shown to protect

both the dog and rat subjected to hemorrhagic shock.[32,33] In these studies, a given hypotensive level was maintained by graded hemorrhage. Prior administration of chlorpromazine resulted in a significant increase in the number of survivors, except when an extremely severe hypotensive episode had been induced. However, the volume of hemorrhage required to maintain the desired hypotension was significantly reduced in the pretreated animals. This does not necessarily imply that chlorpromazine exerted a protective action against hemorrhagic shock. Rather, it seems more plausible to assume that the drug, by lowering blood pressure through its pharmacologic action, reduced the amount of bleeding required to produce any given degree of hypotension.

Administration of chlorpromazine immediately after the hemorrhage gave no protection to the animals.[32] Moreover, in other studies[34,35] the use of chlorpromazine had a deleterious effect on survival of dogs given the drug either soon before or immediately after a single hemorrhage of 4% body weight or after a hemorrhage sufficient to maintain a given hypotensive level. These experiments, more directly applicable to Cases 1 and 3, were interpreted as demonstrating conversion of the hemorrhagic shock into an irreversible state by use of chlorpromazine. "Since a predetermined, standard amount of blood was removed from the animals, dilation of the vascular bed by autonomic blockage (i. e., chlorpromazine administration) either before or after hemorrhage, would result in lower pressures and a decreased ability for adjustment by the autonomic nervous system to the stress."[34]

In view of this experimental and clinical evidence, further emphasis concerning the possible hypotensive effects of promazine, and of other phenothiazine tranquilizers, seems warranted. The occurrence of this complication in patients whose cardiovascular and hepatic status is normal may present only a bothersome and rarely dangerous problem, as in Cases 5 and 6. Patients whose sympathetic responsiveness is diminished, as in Case 7, may be more prone to develop this side-effect. Its occurrence in patients with impending vascular collapse or severe hepatic dysfunction, as in Cases 1 through 4, however, may be much more serious and may lead to an irreversible collapse markedly resistant to pressor agents. This sequela must be considered in the routine use of tranquilizing agents for patients who are restless, nervous, apprehensive, or tremulous, for these may be manifestations of impending peripheral vascular collapse. The presence of a precariously balanced sympathetic nervous system may well be reflected in the cases of significant hypotension following use of promazine here reported. The rarity of serious hypotension in the vast majority of patients given promazine is probably explained by the absence of a markedly compromized peripheral circulation.

Summary and Conclusions

The development of hypotension following administration of promazine (Sparine) is illustrated by seven case reports, in three of which this event preceded death of the patients. Review of experimental and clinical reports on chlorpromazine reveals a number of factors which may be related to the occurrence of this complication. Caution is advised in the routine use of phenothiazine tranquilizers, particularly in patients in borderline vascular collapse.

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Lymphocyte Production and Turnover

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In recent years there has been a great deal of effort expended in attempts to determine the "life span" of white blood cells. With the development of isotopic labeling techniques it was felt by many that finally real progress was being made and that definite figures could be given for the survival time of lymphocytes and granulocytes. Accordingly, most authorities now accept 9 to 13 days as the life span of the granulocyte[1,2] and perhaps 200 days for the lymphocyte.[3]

However, to accept 200 days as the life span of the lymphocyte, one must reconcile this with a large background of sound experimental work extending back more than 30 years, which indicates that circulating mass of lymphocytes turns over very rapidly, implying a short life span.

These earlier conclusions were based on two main observations: (1) the comparatively huge numbers of lymphocytes entering the vascular tree via the thoracic duct, where the daily output of lymphocytes alone is sufficient to replace the circulating blood lymphocytes one or more times, depending on the animal,[4-10] and (2) the rapid disappearance of transfused lymphocytes from the blood.[5,11-13]

In an attempt to resolve this confusion, we have used a combination of isotopic and nonisotopic procedures to study the rate of appearance of lymphocytes in the thoracic duct and the peripheral blood of dogs. Lymphocytes have been labeled in vivo[14,15] and in vitro for these studies.

The production and disappearance of the lymphocyte from the blood are, of necessity, closely integrated with the function and fate of the cell. The function and fate of the lymphocyte have long been the subjects of much controversy and many theories.[9,16-22] One of the most intriguing has been the suggestion, largely on morphologic grounds, that the lymphocyte leaves the blood and enters the bone marrow, where it becomes a blast cell capable of differentiation into other cell types.[16,18,21] Work is to be reported which demonstrates that the lymphocyte, as it enters the blood, is actively synthesizing DNA, as shown by P^{32} incorporation. This recognition that lymphocytes as they exist in the thoracic duct are capable of rapid incorporation of P^{32} into DNA represents a major technical advance in the study of the physiology of these cells. Similar findings have been recently reported by Cronkite, who employed tritium-labeled thymidine as a DNA label.[23] Data will also be presented indicating that the labeled lymphocyte enters the bone marrow after a very brief sojourn in the circulating blood after its entry from lymphatics. Although we have no evidence of the fate of the lymphocyte in the marrow, this study will show that significant numbers subsequently enter the peripheral blood as lymphocytes.

Method

Ten dogs were given P^{32} intravenously, and at varying time intervals after administration of the isotope the dogs were subjected to thoracic duct

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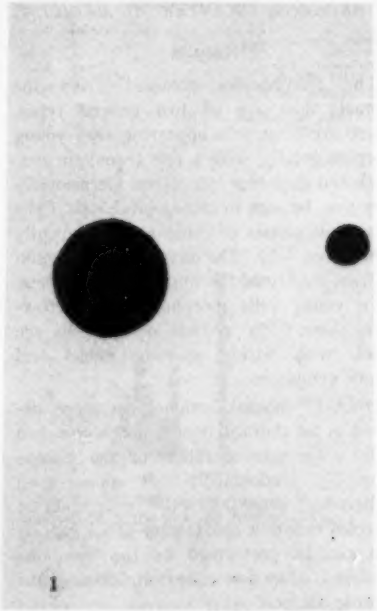
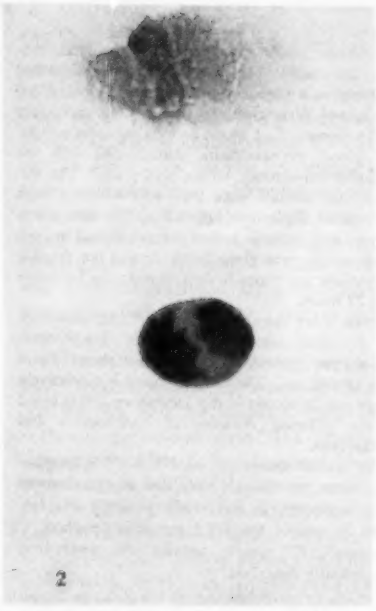
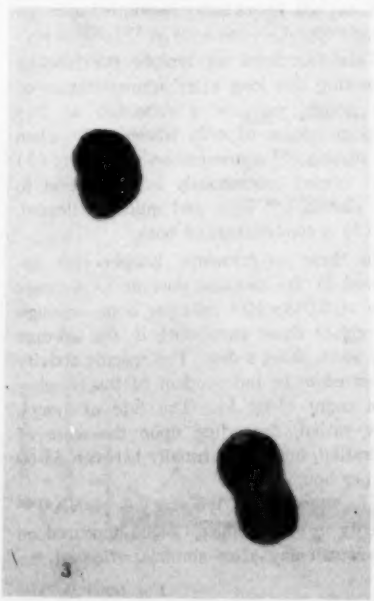
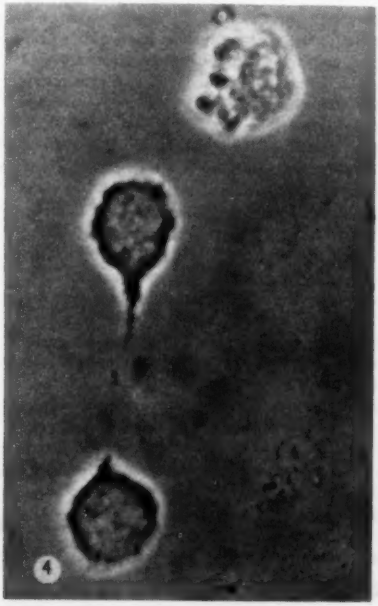




Figs. 1-4.—Various phases of mitosis seen in lymphocytes obtained from the thoracic duct. Figure 1 also demonstrates a small lymphocyte, and Figure 3 shows a large immature lymphocyte. These are smears obtained directly from the thoracic duct, dried immediately, and stained. Figure 4 is a phase-microscope view of lymphocytes shortly after division.





cannulation under pentobarbital (Nembutal, Abbott) anesthesia. The technique has been described in detail in a previous publication.[16] Frequent cell counts and Wright-stained smears were performed on the thoracic duct lymph as well as on the peripheral blood. Smears were also stained with the methyl-green-pyronin nucleic acid stain.[26] The experimental animals were kept well hydrated with intravenous fluids including saline, 5% dextrose in water, and protein hydrolysates. Penicillin and streptomycin were given daily. It was not feasible to continue any thoracic duct cannulation for more than 72 hours.

Seven other dogs were given P^{32} intravenously. At frequent intervals thereafter lymphocyte-granulocyte separations of the peripheral blood were carried out. The method[25] used is a relatively simple one developed in this laboratory and is based on the differing densities of lymphocytes and granulocytes.

The rate of appearance of DNA-P^{32} in lymphocytes from the thoracic duct and of lymphocytes and granulocytes in the peripheral blood was followed by use of the DNA-extraction method of Simmons.[20] P^{32} specific activity was determined as previously described.[24]

For the in vitro labeling of lymphocytes lymph was obtained from the thoracic ducts of dogs. Aseptic precautions were observed as far as possible, and tetracycline, 2.5μg. per milliliter, was added to each tube. After the addition of 15μc. of P^{32} for each billion lymphocytes, the lymph was incubated with constant gentle motion at 37 C. Smears and cell counts were made at frequent intervals. Interestingly enough, lymphocyte counts before and after 16 hours' incubation were approximately the same.

After incubation, the lymph was centrifuged and the cells were resuspended in buffered saline and injected over a 15-minute period into the same animal from which the collection was obtained. Lymphocytes were injected in amounts of 0.1 to 0.15×10^{10}. Bone marrow aspirations were performed at appropriate intervals. In these preliminary experiments no attempt was made to quantitate the marrow, although the volume of marrow plated for isotope activity was constant. It was assumed that any radioactivity found in the bone marrow aspirates would represent activity largely introduced by the labeled lymphocytes. However, for purposes of convenience in handling and concentration the aspirates were ashed. Approximately 2 to 3 ml. of marrow was obtained on each occasion.

Simultaneously with each bone marrow aspiration the animals were bled for leukocyte DNA-P^{32} as described previously.[24,25]

Results

The lymphocytes obtained from the thoracic duct are of two general types. There are large cells appearing very young morphologically, with a fine chromatin network and dark blue cytoplasm. Occasionally they may be seen in chains or clumps. Cells in various phases of mitosis are frequently seen (Figs. 1-4). The methyl-green-pyronin Y stain confirmed the impression that these were young cells morphologically. However, about 65% to 75% of the cells are small, with darkly staining nuclei and scanty cytoplasm.

DNA-P^{32}-labeled lymphocytes were detected in the thoracic duct lymph within two hours after administration of the isotope (Fig. 5). Undoubtedly they appear even earlier, but, since 0.04×10^{10} cells must be collected before a satisfactory DNA extraction can be performed by the technique employed, time for collection becomes the limiting factor.

After reaching a peak in six to eight hours, the DNA-P^{32} falls off. However, some activity is still detectable (Fig. 6) as late as 160 hours after administration of the isotope.

This low level of lymphocyte labeling persisting this long after administration of the isotope may be a reflection of (1) gradual release of cells labeled only when the plasma P^{32} concentration was high; (2) cells labeled continuously in proportion to the plasma P^{32} level and quickly released, or (3) a combination of both.

In these experiments, lymphocytes appeared in the thoracic duct at an average rate of 0.043×10^{10} cells per hour—enough to replace those circulating in the average dog seven times a day. The specific activity appeared to be independent of the lymphocyte count (Fig. 5). The rate of lymph flow varied, depending upon the state of hydration, but it was usually between 35-60 cc. per hour.

The peak of lymphocyte DNA-P^{32} activity in the peripheral blood appeared on the fourth day after administration of the

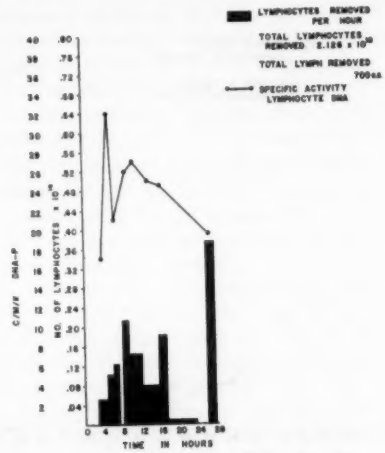

LYMPHOCYTES REMOVED PER HOUR
TOTAL LYMPHOCYTES REMOVED 2.126 x 10^10
TOTAL LYMPH REMOVED 7000cc
SPECIFIC ACTIVITY LYMPHOCYTE DNA
C/M/M DNA-P
NO. OF LYMPHOCYTES x 10^9
TIME IN HOURS

Fig. 5.—DNA-P^{32} specific activity in lymphocytes obtained from the thoracic duct of a dog. P^{32} was administered at Time 0.

isotope. This is identical with the peak for labeled granulocytes in the peripheral blood of dogs, but granulocyte DNA-P^{32}-specific activity is invariably greater (Fig. 7). In the first two days there appears to be no significant difference, although the lymphocyte DNA-P^{32} is frequently slightly higher. A secondary peak occurs on the 18th to the 20th day, the significance of which is not apparent at present.

When P^{32} was incubated with the lymphocytes at 37 C, it was readily incorporated into DNA, and so after 16 hours the specific activity was 25-30 counts per minute per microgram of DNA-P. Morphologically the cells appeared intact, although more degenerated forms were present than in the fresh specimen. In vitro P^{32} incorporation was also demonstrated when lymphocytes in a chylous effusion from a human patient were used.

Preliminary experiments were performed with reinfusion of in vitro P^{32}-labeled lymphocytes into the original donor dogs. Although no quantitation was attempted, significant radioactivity appeared in the bone marrow within 15 minutes, reached a peak in 2 days, then fell rapidly, so by 12 days there was little activity. Radioactivity in the peripheral blood leukocytes (in this preliminary work, no lymphocyte-granulocyte separations were done) appeared during the first day and was very marked on the fifth day.

In one animal, in which it was possible to collect thoracic duct lymph for three hours after an injection of its own P^{32}-labeled lymphocytes, no specific activity

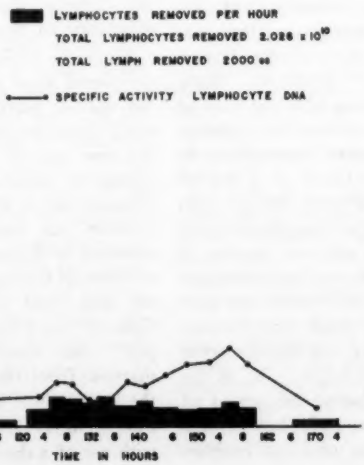

LYMPHOCYTES REMOVED PER HOUR
TOTAL LYMPHOCYTES REMOVED 2.026 x 10^10
TOTAL LYMPH REMOVED 2000 cc
SPECIFIC ACTIVITY LYMPHOCYTE DNA
C/M/M DNA-P
NO. OF LYMPHOCYTES x 10^9
TIME IN HOURS

Fig. 6.—DNA-P^{32} specific activity in thoracic duct lymphocytes after administration of the P^{32} 100 hours prior to cannulation.

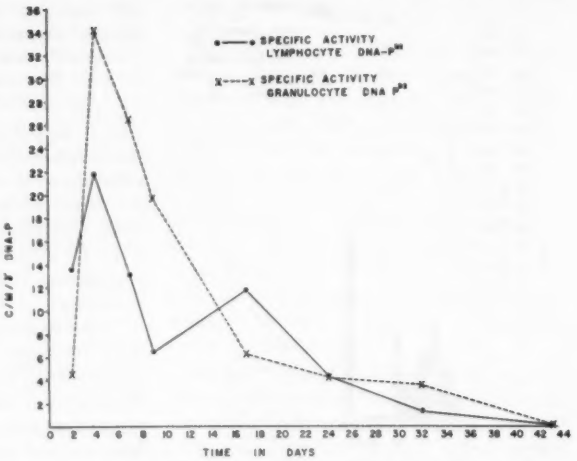


Fig. 7.—The rate of appearance of DNA-P^{32}-labeled lymphocytes and granulocytes in the peripheral blood. The P^{32} was administered on Day 0. It is to be noted that the peak activity for both types of cells occurs at about the same time.

was detected in lymphocytes obtained from the thoracic duct.

Comment

On the basis of this study, several well-known observations have once again been confirmed and some other conclusions have become almost inescapable. It is well established that enough new lymphocytes enter the blood via the thoracic duct to replace those circulating several times every day. These cells require a remarkably short time for DNA-P^{32} incorporation—less than two hours after administration of the isotope as shown by DNA-P^{32} extraction. Many are young cells morphologically and may be observed in various phases of mitosis. Osgood has made similar observations in the lymphocytes from blood of a normal human adult.[27] Furthermore, the in vitro incubation of thoracic duct lymphocytes with P^{32} showed that these cells are capable of DNA-P^{32} incorporation, a property thought to be present only in cells which will later divide.[28-30] This must mean that lymphocyte growth, maturation, and division occur not only at the site of origin, i. e., in the lymphoid tissue, but during the period of transport to the blood as well. Indeed, data from in vitro incubation of *blood* lymphocytes from normal dogs and humans indicate that even circulating lymphocytes are capable of some DNA synthesis, albeit at a very low level as compared with those in the thoracic duct. This finding, which we feel is extremely significant, enormously complicates the interpretation of isotope data, as reported by Hamilton,[31] Osgood et al.,[32] Ottesen,[2] Kline and Cliffton,[1] and Coassin and Kline,[33] in terms of "life span" of the cell. We do not believe that any of the isotope data yet presented permit estimation of lymphocyte life span.

Since the number of lymphocytes in the peripheral blood remains relatively constant, the number leaving the vascular tree must equal those entering over any given period. No one has, as yet, been able to offer a completely satisfactory explanation of the ultimate fate of the lymphocyte. This whole problem has been well reviewed[9,19] and need not be discussed here. However, some workers in the field are beginning to accept the idea, first proposed by Jordan and Speidel,[16] in 1923, and supported by Yoffey,[22] that lymphocytes enter the bone marrow from the blood, where they have the potentiality of becoming blast cells. Farr,[18] in 1951, reported similar findings with use of a dye to label lymphocytes. The

preliminary studies reported here with transfusion of autologous P^{32}-labeled lymphocytes demonstrates that lymphocytes leave the blood and return to the bone marrow. However, the question of whether these cells then become blast cells remains unanswered.

The occurrence in the peripheral blood of maximum lymphocyte DNA-P^{32} activity on the same day as for the granulocytes after in vivo labeling may be interpreted as further evidence that lymphocytes leave the blood quickly after entry from lymphatics, enter the bone marrow, and then are released simultaneously with the segmented neutrophils. We have no data at the present time as to the per cent of lymphocytes leaving the marrow as compared with the number entering. However, this approach, coupled with radioautographic histologic techniques, should provide a more definite answer as to whether lymphocytes are multipotential cells. It is possible, as has been suggested by others, that the lymphocyte may contribute nuclear material to other cell lineages during their development. Such possibilities cannot be resolved except by direct observation of specifically labeled cells.

It is interesting to note that there is no early sharp rise in peripheral blood lymphocyte DNA-P^{32} specific activity, in spite of the fact that the thoracic duct lymphocyte DNA-P^{32} activity is very high in the first few hours. Since there is no reason to believe that cells labeled in vivo are lost preferentially from the blood, the most important factor in determining the steepness of the curve for specific activity in the peripheral blood would be the ratio of the number of labeled cells lost to the unlabeled ones. Reentry of labeled lymphocytes via the thoracic duct probably does not occur, since one would then not expect the lymphocyte DNA-P^{32}-specific activity in the peripheral blood to fall off rapidly. Furthermore, in one period of observation of three hours following the administration of labeled lymphocytes, no radioactivity appeared in the thoracic duct.

One needs only to read the accumulated literature on the lymphocyte to realize that the purpose and fate of this cell remain mysterious. No one has been able to ascribe to it, in contrast to the granulocyte, a definite function. There is some suggestion in the preliminary data presented in this investigation that the lymphocyte may be important in the fundamental bone marrow function of cell reproduction.

Summary

The production rate of DNA-P^{32}-labeled lymphocytes in the thoracic duct of dogs has been studied, and their rate of appearance in the peripheral blood has been followed.

Lymphocytes develop rapidly, enter the blood stream quickly, but spend a relatively short time in the intravascular compartment.

Thoracic duct lymph contains many young cells capable of division and DNA incorporation of P^{32}.

Preliminary work indicates that when autologous thoracic duct lymphocytes are labeled and then reinjected radioactivity appears almost immediately in the bone marrow.

Department of Medicine, School of Medicine, University of California Medical Center (24).

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Pulmonary Tuberculosis Associated with Carcinoma of the Lung

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The principle of explaining all of the symptoms and findings of a patient as manifestations of the same disease entity is undoubtedly justified in the majority of cases. All physicians are familiar with exceptions to the rule, particularly in older patients in whom multiple diagnoses are not uncommon. Indeed, the early recognition of two major diseases in the same patient presents a real challenge, particularly if both major diseases involve the same organ.

Coexistence of pulmonary tuberculosis and carcinoma of the lung is well known. In the cases reported a common feature is the late diagnosis of the neoplasm, with a paucity of survivals because the carcinoma is so far advanced that successful treatment cannot be applied. Moreover, many cases are recognized only at postmortem examination.

Famous pathologists have tried to correlate the etiology of the two diseases in one way or another and sometimes in exactly opposite ways. Rokitansky supported the theory of antagonism, which held that tuberculosis was an effective antagonist against carcinoma of the lung. Treatment of carcinoma with tuberculin was applied with "encouraging results." [2] Many years later Ewing stated conversely that tuberculosis was the chief etiological factor of bronchogenic carcinoma.[4] He later admitted, "Old tuberculosis is of diminishing importance as an etiologic factor of bronchogenic carcinoma." [5] Today it is generally accepted that the two diseases are associated only coincidentally. It is known that a disease which lowers the general resistance can activate or aggravate pulmonary tuberculosis. This, of course, applies not only in carcinoma but in other diseases, such as diabetes, Hodgkin's disease, and leukemia.

There are two factors which make the problem of coexisting pulmonary tuberculosis and bronchogenic carcinoma one with which we are confronted increasingly. First, the distribution of active pulmonary tuberculosis is moving constantly toward the older groups. Second, carcinoma of the lung is, for reasons not to be discussed here, increasing in frequency and constitutes, according to newer statistics, at least 10% of all malignant tumors, while in Rokitansky's time it was accepted as less than 1%. The practical point to remember is that the two diseases coincide more frequently now than in the past. Any decrease in deaths or any appreciable increase in survival rate has to come by way of earlier diagnosis and treatment. Illustration of the following 10 cases will demonstrate a few useful points.

Report of Cases

CASE 1.—A 55-year-old man was well until 1953, when he began to notice weight loss and had occasional hemoptysis, with constant fatigue and anorexia. Chest x-ray examination, in 1954, was reported as compatible with tuberculosis. Antituberculosis drug therapy was given at this time. Pneumoperitoneum therapy was started in October, 1954. His first hospital admission was in July, 1955. Chest roentgenogram at admission (July 25, 1955) showed infiltration in the right upper lobe and a small area of infiltration in the left upper lung field, both cavitary. Four sputum examinations were positive for tubercle bacilli. Follow-up radiograph, on Dec. 26, 1955, showed a remarkable clearing of the right upper lung disease, while

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there was a new dense infiltration in the left upper lobe associated with left mediastinal adenopathy and a 3.5 cm. cavity containing an air-fluid level (Fig. 1). A left phrenic crushing operation was done in 1956. The patient was admitted to the Ohio Tuberculosis Hospital on April 2, 1957. Chest roentgenogram, on April 4, 1957, showed further increase in the left mediastinal adenopathy and also two distinct cavities containing air-fluid levels in the left upper lung field, located anteriorly. The left upper lobe showed underaeration. The bronchogram made after admission of the patient showed complete obstruction of the left upper lobe bronchus, indicating malignant tumor with abscesses distal to the obstruction (Fig. 2). A left exploratory thoracotomy was undertaken on

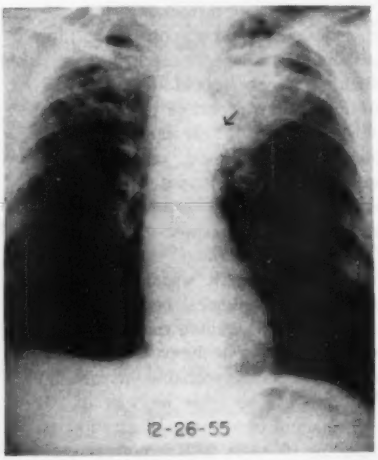

Fig. 1

April 30, 1957, and showed a nonresectable tumor of the left lung. The patient died on May 19, 1957. Autopsy findings showed bronchogenic carcinoma of the left upper lobe bronchus, with metastases to the left hilar nodes and left lower lobe; bilateral fibroid and fibrocaseous pulmonary tuberculosis, with persistent cavity; bilateral diffuse and bullous pulmonary emphysema; hypertrophy and dilatation of the right ventricle (cor pulmonale). There was no evidence of distant metastases.

Case 2.—A 64-year-old man. The illness began with a persistent productive cough in 1949. Chest roentgenogram, on Nov. 10, 1949, showed nodular and linear infiltration in the right upper lung, with a 3 cm. cavity in the right apical area (Fig. 3). He was treated with intermittent drug therapy and hospital care for tuberculosis from that date until the admission date of April 24, 1953. Numer-

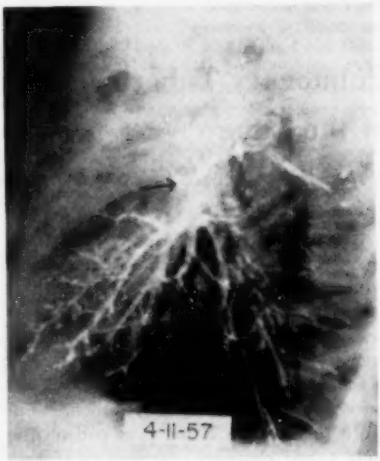

Fig. 2

ous bacteriologic examination revealed typical acid-fast bacilli. Prior to final hospitalization a clinical diagnosis was made of tuberculosilicosis, based on his lifetime occupation as a stonecutter. Chest film, of Dec. 26, 1951, showed a new infiltration in the left lower lung field, with prominence of the left hilum, measuring 7.4 cm., while in November, 1949, it had measured 6.2 cm. (Fig. 4). Late in 1953, about five months before the final admission, there was an onset of aching left lateral

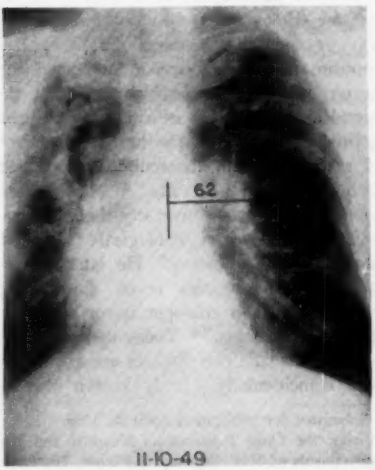

Fig. 3

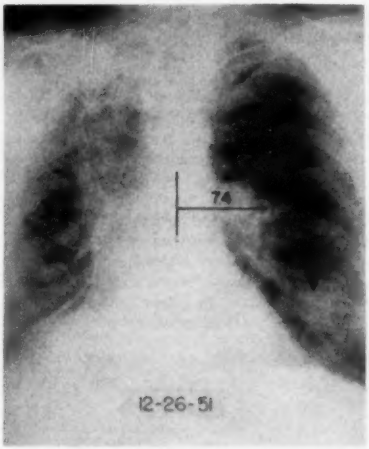

Fig. 4

lower chest pain, marked anorexia, severe productive cough, and progressive weight loss of 30 to 35 lb. Chest roentgenogram at the time of admission (April 25, 1953) showed definite further increase in the left lower lobe mass associated with enlarged left hilum, while there was decrease in the right upper lobe infiltration and also decrease in the size of the right upper lobe cavity. At the time of admission there was evidence of osteolytic lesions in the 10th and 11th ribs posteriorly on the left side. Biopsy specimen from a subcutaneous tumor on the left thigh showed metastatic undifferentiated carcinoma. This was 17 months after the first manifestations of malignancy were present in his chest. Owing to the widespread metastases the patient was considered as inoperable. The patient died on July 8, 1953. Autopsy showed bronchogenic carcinoma of the left lower lobe with extension to the left upper lobe. There were multiple metastases to liver, left ribs, vertebrae, adrenals, hilar lymph nodes, and also left pleura. Fibrocavitary tuberculosis, right lung, was present with tuberculosilicosis.

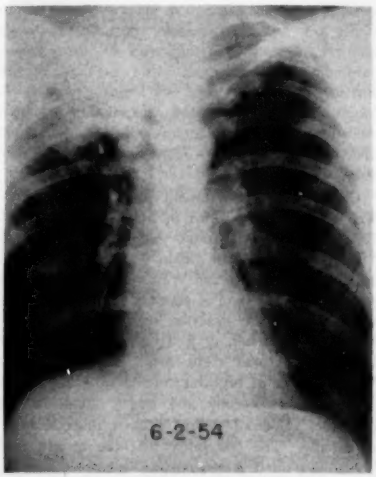

Fig. 5

CASE 3.—A 50-year-old man was treated for one year in a sanatorium for far-advanced pulmonary tuberculosis, proven by repeated smears and cultures. Chest roentgenogram, on June 2, 1954, (Fig. 5) showed extensive confluent infiltration in the right upper lobe and also ill-defined infiltration in the left apex, which improved considerably in two and one-half months. At this time a prominence of the left hilum was noted. This patient was discharged on Feb. 3, 1955, with his tuberculosis markedly improved and with the recommendation of surgery for the residual disease of his right upper lobe. He had a follow-up examination on June 9, 1955 (Fig. 6), which revealed obvious left hilar adenopathy and an infiltration in the left base medially. These findings were not appreciated until the next examination, three months later. The patient was admitted to the Ohio State University Hospital for further evaluation. At the time of surgery an unresectable squamous-cell

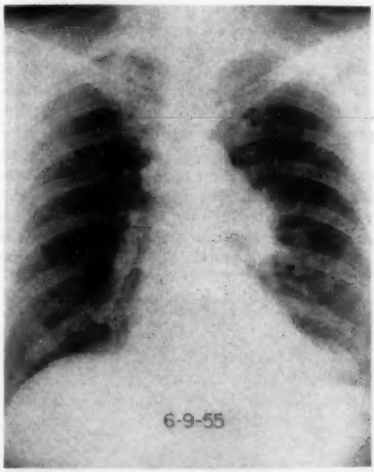

Fig. 6

carcinoma of the left lung invading the left pulmonary artery was found. This was approximately 16 months after the first signs of his left hilar adenopathy were present.

CASE 4.—A 62-year-old man developed symptoms of productive cough and weight loss in February, 1955. He did not have any chest roentgenograms until July, 1955, at which time there was evidence of pleural fluid in both bases and nodular lesions scattered throughout both lung fields. The patient was admitted to the hospital on July 29, 1955. Aspirated fluid from the right pleural space and sputum smears and cultures showed acid-fast bacilli. After August, 1955, his sputum was persistently negative for Mycobacterium tuberculosis. In spite of this, his condition was deteriorating. A definite mass had appeared in the right hilum. Bronchoscopy with right bronchial biopsy showed poorly differentiated squamous-cell carcinoma. The patient was not a surgical candidate and was referred for palliative x-ray therapy. He died on April 27, 1956. Autopsy confirmed the diagnosis of active pulmonary tuberculosis and bronchogenic carcinoma with metastases to the liver.

CASE 5.—A 63-year-old barber had a cough, with a few teaspoonfuls of yellow sputum for the past several years. His previous chest roentgenogram showed fibrocalcific changes in the right apex. Because of a new infiltration, discovered in a follow-up radiograph in April, 1955, he was admitted to a sanatorium. His sputum studies were negative for acid-fast bacilli. His P. P. D. skin test was postive, and the histoplasmin skin test was negative. The patient was transferred to the Ohio Tuberculosis Hospital on Sept. 6, 1955. The admission roentgenogram showed a mass in the region of the anterior segment of the right upper lobe. A bronchogram was performed on Sept. 15 (Fig. 7). This showed obstruction of tertiary branches of all segmental bronchi of the right upper lobe and narrowing of the bronchus of the anterior segment. A diagnosis of bronchogenic carcinoma was suggested. Bronchial biopsy confirmed the impression. A right upper lobe lobectomy was performed. Examination showed well-differentiated squamous-cell carcinoma and apical scar which was "entirely compatible with tuberculosis. . . ."

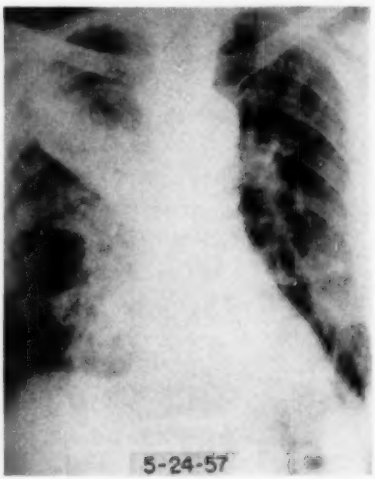

Fig. 8

Fig. 7

CASE 6.—An 85-year-old man was apparently well until five days prior to admission to the Ohio State University Hospital. He had hemoptysis of 1 pt. of blood. Hemoglobin was 15.0 gm.; RBC count was 5,400,000, and WBC, 5,600. Chest roentgenogram at the time of admission (Fig. 8) showed atelectasis of the anterior segment of the right upper lobe, containing a 3 cm. cavity with fluid level. There was right mediastinal adenopathy. The diagnosis of bronchogenic carcinoma was suggested. Bronchoscopy and biopsy confirmed the diagnosis. Sputum studies showed tubercle bacilli repeatedly. The possibility that the bronchogenic tumor activated a preexisting tuberculous lesion was considered. The patient was discharged.

Surgery was impossible due to the patient's age and extension of the disease to the mediastinum.

CASE 7.—A 55-year-old man developed weight loss, anorexia, and night sweats in 1952. He received intermittent hospital care after this date. Sputum was positive for tubercle bacilli. Roentgenogram of his chest on April 12, 1954, showed fibrotic nodular and linear infiltration, with scattered calcified foci in the left upper lung field and a slight upward retraction of the left hilum. In April, 1955, the patient had hemoptysis, although sputum had been negative for acid-fast bacilli since May, 1954. Chest x-ray film (Fig. 9) showed no parenchymal changes. It was not appreciated at this time that there was an enlargement and fullness of the left hilus in comparison with the

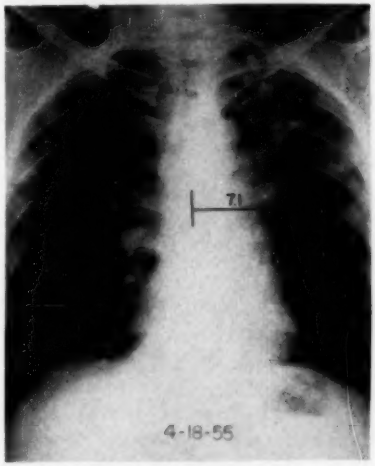

Fig. 9

roentgenogram one year before. Roentgenogram one year later, in April, 1956, showed atelectasis of the left upper lobe. The patient was still receiving antituberculosis drugs, and pneumoperitoneum therapy was started. He had repeated episodes of hemoptysis. On Oct. 17, 1956, the patient was admitted to the Ohio Tuberculosis Hospital. The chest roentgenogram at the time of admission showed atelectasis of the left upper lobe, and bronchogenic carcinoma was suggested in addition to the old tuberculosis. The impression of tumor was confirmed in a subsequent bronchogram (Fig. 10). This showed complete block of the left upper lobe bronchus, with the superior segment of the lower lobe extending into the apical region. A bronchial biopsy of the left upper lobe bronchus confirmed the diagnosis. The patient had a left pneumonectomy. The pathological diagnosis was

Fig. 10

poorly differentiated squamous-cell carcinoma arising from the left bronchus, with extension to the mediastinum and atelectasis distal to the obstruction; chronic inactive, fibroid, and fibrocaseous pulmonary tuberculosis.

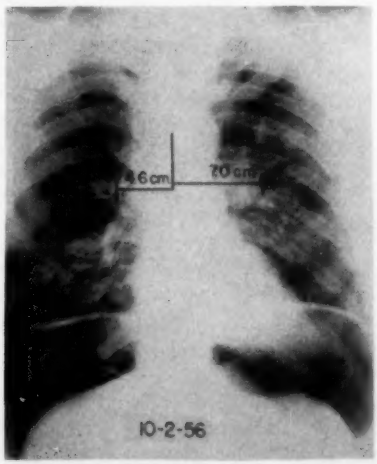

Fig. 11

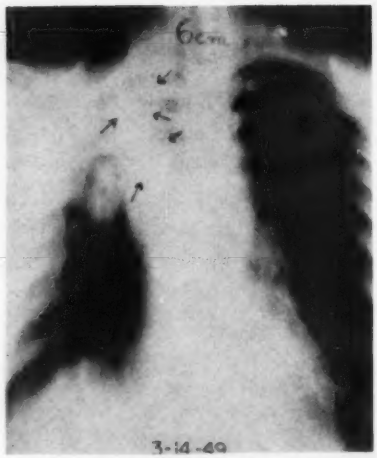

Fig. 12

Case 8.—A 57-year-old man was well until the winter of 1954, when a routine chest roentgenogram showed infiltration in the left upper lung field, with a small cavity in the infraclavicular area. Sputum examination was positive for acid-fast bacilli. In January, 1955, he was hospitalized and given antituberculosis therapy. He had a left phrenic crushing operation in June, 1956. His general condition improved, and he was discharged in October, 1956. Roentgenogram on Oct. 2, 1956, showed definite hilar adenopathy on the left side, the left hilum being more than 2 cm. wider than the right, with an increase in the size of the left hilum in comparison with the previous examination (Fig. 11). Seven months later the patient was rehospitalized. A biopsy specimen from the left bronchus showed bronchogenic carcinoma. The patient was admitted on June 4, 1957, to the Ohio Tuberculosis Hospital, at which time a large mass in the left hilar area was present. Biopsy from the left bronchus showed poorly differentiated squamous-cell carcinoma. Bone survey showed metastatic involvement of the spine.

Case 9.—A 70-year-old man had a history of pulmonary tuberculosis, with cavities in the right upper lung. He was admitted on Aug. 19, 1948,

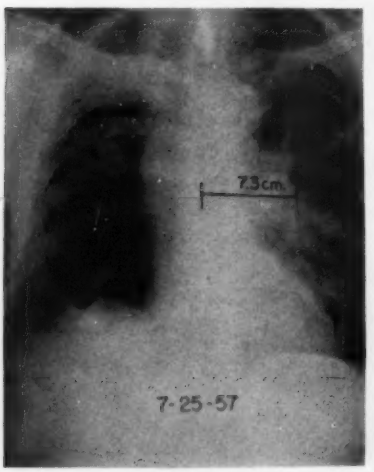

Fig. 13

Fig. 14

to a sanatorium, with the diagnosis of far-advanced pulmonary tuberculosis, and stayed there for approximately seven months. Laminagram on March 4, 1949, showed multiple cavities in the right upper lung (Fig. 12). He was readmitted in January, 1954, and found to have tubercle bacilli in his sputum. Laminagram on Feb. 23, 1954, showed residual cavities in the right upper lobe. Drug therapy was given and sputum converted. He was given a disciplinary discharge on May 22, 1954. The patient sought medical care on July 6, 1957, when he had a chief complaint of epigastric pain and was treated for duodenal ulcer. He was transferred to the Ohio Tuberculosis Hospital for further evaluation. Chest roentgenogram on July 25 (Fig. 13) showed cavitary disease in the right upper lobe and left hilar adenopathy associated with a soft tissue mass in the left infraclavicular area. A

malignant tumor on the left side with ipsilateral hilar adenopathy was suggested. Cytological studies of sputum showed malignant cells. Lymph node biopsy from the left supraclavicular area showed poorly differentiated squamous-cell carcinoma. Upper gastrointestinal studies showed duodenal ulcer. The patient died on Oct. 21, 1957. Autopsy findings showed bronchogenic carcinoma, with metastasis to aortic lymph nodes, liver, adrenals, and vertebrae. There was fibroid and fibrocalcific pulmonary tuberculosis in the right upper lobe.

CASE 10.—A 54-year-old man was in a sanatorium from August, 1950, to June, 1951, with a diagnosis of pulmonary tuberculosis, proven by sputum studies. On July 17, 1956, he was readmitted wih chief complaints of cough, weight loss, and weakness for the past 10 months. Chest roentgenogram on July 17 (Fig. 14) showed dense infiltration in the right upper lobe, with upward retraction of the right hilus due to an old tuberculous process. The left hilus was enlarged more than 2 cm. in comparison with the right one, and there was a soft tissue mass in the left midlung field adjacent to the left hilus, highly suggestive of bronchogenic carcinoma. The next examination, 16 months later, on Nov. 19, 1957, showed further enlargement in the left hilus and left midlung field mass. There was also destruction of the sixth and seventh right ribs, associated with a soft tissue mass in the right lateral chest wall, found to be a metastatic tumor. The right upper lobe residual fibrotic disease showed no change.

Comment

In 6 of the above 10 cases the first manifestation of carcinoma was unilateral hilar lymph node enlargement. This is in accord with the findings of Rigler, who pointed out that this very important sign is commonly overlooked and is usually present before symptoms appear.[11] The problem is not one of diagnosis but of detection. To measure the transverse diameter of the hilus, we accept as the medial measuring location a point on a vertical midthoracic line bisecting the horizontal transthoracic diameter at the aortic arch and at the level of the diaphragm. The lateral border of the hilus is considered as the margin of the hilus farthest from the midline but not including the first branching of each pulmonary artery. It is true that the determination of the lateral margin is not interpreted the same by every observer, but results of independent measurements showed that the difference is not significant.[11] Prerequisite for an accurate measurement is that in the posteroanterior roentgenogram the patient is well positioned without significant rotation. To ascertain that the hilar enlargement is actual and not due to projection of a pulmonary lesion at this level, as from the superior segment of the lower lobe, a lateral view is needed.

Obliteration of the medial aspect of the pulmonary artery does not increase the transverse diameter of the hilus but gives an "appearance of solidity," as Rigler points out. Minor changes in the transverse diameter of the hilus are more impressive to the practiced eye, which has the ability to appreciate volume changes of the hilus (Case 3, Figs. 5 and 6). In addition, it should be emphasized that it is significant when study of roentgenograms shows an enlarging hilus, no matter what the absolute transverse diameter may be. It is abnormal for a hilus which measured 4.0 cm. to become 6.0 cm. in diameter, in spite of the fact that for another person a 6.0 cm. hilus may be normal.

Conditions other than carcinoma can produce unilateral adenopathy, although these conditions are not frequent in older age groups. Active reinfection tuberculosis in adults seldom exhibits radiologically enlarged hilum nodes of tuberculous origin. Detection of hilar adenopathy is significant because then other more accurate diagnostic procedures may be carried out. Laminagraphy, bronchography, bronchoscopy, and cytology may be helpful in clarifying the cause of the enlarged hilus. Lymph node biopsy should be undertaken if simpler procedures fail to disclose the diagnosis. The important fact is that these studies will not be performed unless the hilar adenopathy is detected. A hilus greater than 5.5 cm. in transverse diameter is suspicious and above 7.0 cm. should be considered abnormal and further evaluated. A difference of more than 2 cm. between the two hila should also be considered as abnormal (Cases 8 and 10).

In Case 3 the hilar adenopathy was not appreciated for a period of more than one year. Similar delay was noticed in other cases.

In some instances where hilar adenopathy is not present, the first manifestation of carcinoma may be the appearance of a pulmonary infiltrate near to or remote from the tuberculous lesions. The presence of such a lesion within the normally air-containing lung parenchyma is easy to detect. This may persist or increase in spite of the fact that the tuberculous disease is improving, cavities are closing, and the sputum of the patient is converted to a "negative" status (Case 8). This should suggest the possibility of a second disease, and malignancy should be the first consideration.

Tuberculosis patients often have a useful set of x-ray films. These will allow careful comparative study in answering the following specific questions: 1. Is the new infiltration associated with ipsilateral hilar adenopathy? 2. Is the new infiltration increasing in size in spite of treatment? 3. Does it contain calcium of the laminated or the so-called popcorn type, both of which are highly unlikely to be associated with malignant lesions? 4. Is metastatic bone involvement already present? 5. Has any new cavity appeared, particularly peripheral to a hilar or mediastinal mass (Cases 1 and 6)? 6. Is the new lesion located anteriorly (Cases 1 and 5)?

The clinical picture of the patient must be taken into consideration also. A unilateral wheeze which the patient did not have before is significant and should indicate a partial bronchial occlusion. Unexpected hemoptysis or blood-streaked sputum require investigation. Weight loss, anemia, and other symptoms which occur while the tuberculous process is improving radiologically will arouse the alert physician to the possibility of bronchogenic carcinoma.

Summary and Conclusion

Ten cases of coexistent pulmonary tuberculosis and carcinoma of the lung are presented.

The increased frequency in the coincidence of these two major diseases is of practical importance.

The main signs which can lead to an early diagnosis of carcinoma of the lung are briefly described.

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The Hemophilioid States

The Practical Application of Present-Day Concepts of Blood Coagulation to Diagnosis and Treatment

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During the past decade there has developed an aura of growing alarm and bewilderment at the progressive complexity of blood coagulation concepts. In the face of this concern, it would seem desirable to review briefly the nature of these concepts and to discuss their practical applications in general medical practice, with particular emphasis on the hemophilioid states.

The hemorrhagic disorders may be divided into three etiologic groups.

Etiologic Groups of Hemorrhagic Disorders

Congenital Hemophilioid Disorders[1-21] (Table 1). These are ordinarily understood to be hemorrhagic disorders that clinically resemble hemophilia resulting from a genetically determined deficiency or inactivity of a factor in plasma which is necessary for an effective prothrombin-converting and fibrin-forming mechanism.[1]

In this communication hemophilia will be included under the heading of a congenital hemophilioid state, although this is not strictly in accord with the common usage of this term. Acquired hemorrhagic states[22-26] closely resembling hemophilia are occasionally seen, and these may be referred to as acquired hemophilioid states: circulating anticoagulants,[22-27] liver disease, vitamin K deficiency (e. g., in newborn,[28] bile duct obstruction, malabsorption), bishydroxycoumarin (Dicumarol) or heparin overdosage, fibrinogenopenia (e. g., secondary to abruptio placentae, concealed accidental hemorrhage, etc.)[29] fibrinolytic reactions (e. g., associated with carcinoma of prostate),[30-32] drug reactions, uremia,[34] and leukemia.[35]

Vascular Purpuras.—In this group are included (1) the primary vascular purpuras, those conditions which can be attributed to intrinsic or extrinsic vascular defects per se, e. g., Schönlein-Henoch purpura, scurvy, senile purpura, telangiectases, etc.; (2) pseudohemophilia (von Willebrand's disease); (3) vascular purpura with qualitative or morphological abnormalities in platelets.

Thrombocytogenic Purpuras.—This group includes (1) the thrombocytopenic purpuras,[36] characterized by a quantitative deficiency in platelets; (2) the thrombocythemias,[37] characterized by an excess of platelets.

In contrast to the thrombocytogenic purpuras and the hemophilioid states, the vascular disorders associated with a prolonged bleeding time and a normal platelet count constitute a very heterogenous group.[38] The majority of the diseases included in this group fall into the category of pseudohemophilia (von Willebrand's disease).

A few years ago it was discovered that some patients who would otherwise have been considered to have pseudohemophilia had low antihemophilic factor (AHF) levels,[39] and the terms pseudohemophilia B[40] and vascular hemophilia[41] were employed to distinguish this entity from other types of pseudohemophilia in which levels of AHF were believed to be normal.

However, a recent restudy[42] of von Willebrand's original cases of pseudohemophilia has revealed that these patients also have a subnormal level of AHF, and so there now seems no justification for the retention of the term pseudohemophilia B or vascular hemophilia. Moreover, in the same study the platelets in von Willebrand's original cases were found to be normal in every respect; von Willebrand and Jürgens[43] were therefore in error when they reported abnormal platelets and renamed the condition "constitutional thrombopathy." Pseudohemophilia (von Willebrand's disease) may now be defined as a hemorrhagic state inherited as an autosomal dominant

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TABLE 1.—*The Congenital Hemophilioid States*

Conditions	Synonyms	Noteworthy Clinical Features	Genetics	Therapy
Hemophilia (AHF deficiency)	Classical hemophilia, hemophilia A	Males affected; family history may be lacking in about 50% of cases; may be mild to severe	Sex-linked recessive	Preferably fresh blood or plasma (less than 24 hr. old): at least 3 pt. whole blood required for hemostatic action in adult; transfused AHF has half-life of 4-11 hr.
PTC deficiency[4-6]	Hemophilia B, Christmas disease	Males affected; incidence of mild cases generally higher than in hemophilia	Sex-linked recessive	Blood, plasma, or serum which may be aged
Factor V[4-6] deficiency	Proaccelerinemia; parahemophilia, Owren's disease	Usually mild; exceedingly rare	Autosomal recessive	Fresh blood or plasma (less than 24 hr. old)
Hageman-factor deficiency[10]	--------	No clinical manifestations	Autosomal recessive	None
PTA deficiency[11]	Rosenthal's syndrome	Mild to severe but no hemarthroses reported	Autosomal dominant	200 ml. of serum or slightly larger amounts of plasma (not more than 7 days old) per 24 hr.
Platelet Factor 3 deficiency[12]	Thromboasthenia	Relatively mild	Probable autosomal dominant	Transfusions of fresh platelet concentrates, fresh platelet-rich plasma, or whole blood collected with special precautions
Stuart-factor deficiency,[13-16]	Stuart-Prower-Factor deficiency, factor XI deficiency	Clinically mild; hemarthroses rare	Autosomal recessive	Blood, plasma, or serum not more than 7 days old
Factor VII[17-18]	Hypoproconvertinemia	Bleeding time frequently prolonged & purpura present; generally mild; hemarthroses rare	Autosomal recessive	Stored blood, plasma, or serum
Prothrombin deficiency[20]	--------	Extremely rare	Not known	Should respond to fresh or stored blood or plasma but not to serum
Fibrinogen deficiency[21]	--------	Clinically mild; hemarthroses rare	Autosomal recessive	Fresh or stored whole blood or plasma; fibrinogen preparations

characterized by a prolonged bleeding time, normal coagulation time, and a low AHF level; the platelets are normal both quantitatively and qualitatively. Recent work [42] has also shown that the prolonged bleeding time in pseudohemophilia can be restored to normal by the administration of AHF-free fractions of normal blood, and so if there is a capillary defect, as is generally believed, this is not necessarily a primary one.

Apart from pseudohemophilia, there are other conditions in which the bleeding time is prolonged and the platelets normal in number. In the majority of these conditions, the AHF level is normal and the platelets show various qualitative abnormalities, thereby differing from pseudohemophilia. The qualitative abnormalities of platelets may include one or more of the following conditions: deficiency in the clot-retraction factor, deficiency of a factor essential for blood thromboplastin formation (Platelet Factor 3), or absence of clumping and deficient pseudopodia formation. These conditions are comparatively rare and the nosological nomenclature confusing and contradictory; therefore, a simple descriptive terminology is recommended. Since these cases appear to have in common a vascular defect, they may accordingly be classified under "vascular purpuras," and the individual disorders may in turn be appropriately qualified, as for example, "vascular purpura with deficiency of the platelet clot-retraction factor." Since this condition was originally described by Glanzmann [44] and is generally known as Glanzmann's disease, this should be stated on the report.

Recent progress in the field of blood coagulation has been clouded by a multiple

TABLE 2.—*Nomenclature of Clotting Factors*

Coagulation Factors	Some Synonyms	Present in Serum	Adsorbed by Certain Salts *	Stability in Stored Blood
Fibrinogen	Factor I	No	No	Stable
AHF	Factor VIII; antihemophilic factor; antihemophilic globulin; AHG	No	No	40%-70% activity lost after 3-wk-storage
Platelets	Platelet Factor 3	No	No	Thromboplastin function probably not diminished
Prothrombin	Factor II.	No	Yes	Stable
Factor V	Proaccelerin; labile factor; Ac-globulin; Ac-G	No	No	Poor
Factor VII	Serum prothrombin conversion accelerator; SPCA; proconvertin	Yes	Yes	Stable
PTC	Factor IX; plasma thromboplastin component; Christmas factor; CF	Yes	Yes	Stable
PTA	Plasma thromboplastin antecedent	Yes	Partly	Stable
Hageman factor	None	Yes	Partly	Stable
Stuart factor	S. F.; Stuart-Prower factor; Factor XI	Yes	Yes	Stable

*Usually aluminum hydroxide or barium sulfate.

and chaotic nomenclature of clotting factors (Table 2). Since this confusion is due, in part, to the use of terms based upon a particular investigator's interpretation of his experimental data or, alternately, on the theory of coagulation in vogue, it is best to avoid those terms which have been given a functional connotation, e. g., "serum prothrombin conversion accelerator," at least until that time when the exact mode of action of these factors is clearly established.

Blood coagulation theories come and go, and at present there is no widely accepted scheme. Since theories are but the blueprints of the research worker, a scheme is presented (Fig. 1) which, although incomplete, brings out all the practical implications of recent progress in the field of blood coagulation and also serves to demonstrate clearly the theoretical basis of two valuable diagnostic tests. It can be seen that there are two pathways, an intrinsic and an extrinsic, both leading to the formation of a final prothrombin conversion factor. The intrinsic system, which reflects the intravascular blood coagulation mechanism, was long neglected, until revived by Macfarlane and his associates.[45,46] These workers suggested that the function of the coagulation factors, with the exception of prothrombin and fibrinogen, was to form a prothrombin-conversion factor, i. e., blood thromboplastin, and the delay in coagulation of whole blood was due mainly to the time required for these factors to react. This hypothesis received strong support when it was shown that incubation of adsorbed plasma,* serum, platelets, and calcium after a latent period of several minutes leads to the development of a thromboplastin more potent than any known

* Plasma treated with aluminum hydroxide or barium sulfate to adsorb prothrombin, PTC, Stuart factor, and Factor VII.

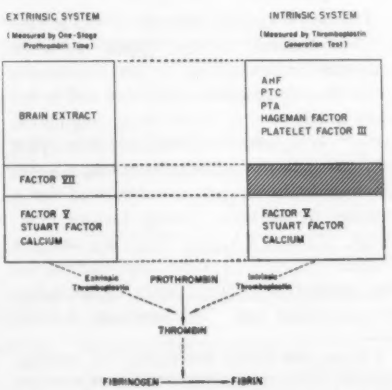

Fig. 1.—The dual-mechanism theory of blood coagulation, based on the one-stage prothrombin time and the thromboplastin generation test. An abnormality in one or both systems usually results in a hemophilioid state.

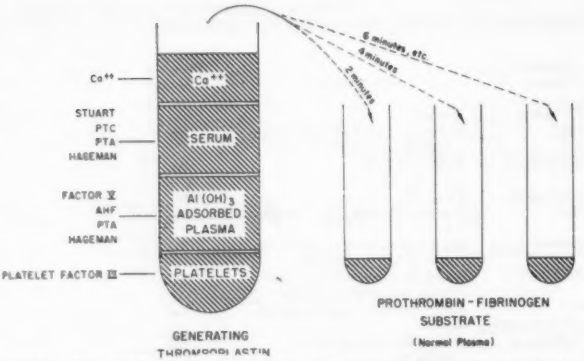

Fig. 2. — Thromboplastin-generation test. Plasma treated with aluminum hydroxide to remove prothrombin, Stuart factor, and PTC and diluted 1:5 is incubated with normal serum (diluted 1:10) platelet suspension and calcium chloride. At short intervals following the addition of the calcium chloride aliquots are removed from the incubation mixture and added to a normal plasma substrate (source of prothrombin and fibrinogen) in the presence of an optimal concentration of calcium, and the clotting times are recorded. The results using test plasma, test serum, and test platelets in the incubation mixture are compared with those using plasma, serum, and platelets from normal blood to establish the presence or absence of a coagulation defect; if a defect is detected then normal blood components are substituted in turn for each of the components of the deficient blood to incriminate the fraction (plasma, serum, or platelets) responsible for the defect in intrinsic thromboplastin formation. For technical details the original paper of Biggs and Douglas[48] should be consulted.

tissue extract. The activity of this material can be measured by its effect on the clotting time of recalcified normal plasma. This procedure, now known as the thromboplastin-generation test (Fig. 2), therefore reflects variations of all the blood thromboplastin components, with the exception of Factor VII.† [47,48] It has led to the elucidation of defects in a number of hemorrhagic disorders and has also proved to be a valuable diagnostic tool.

The better-known extrinsic or tissue system, as reflected by the Quick one-stage prothrombin time (Fig. 3), has also been a great boon to research endeavors and is the most widely used of all the blood coagulation tests.[49] It is, however, a less complete index of clotting-factor deficiencies in that a tissue product, brain extract, is substituted for a number of intrinsic clotting factors (i. e., AHF, PTC, PTA, the Hageman and the Platelet Factor 3 ‡) which are required for the coagulation of blood in the thromboplastin-generation test. This accounts for the fact that in those conditions in which these intrinsic factors are deficient (hemophilia, Christmas disease or congenital PTC deficiency, PTA and Hageman-factor deficiencies, and thrombocytopenia) the one-stage prothrombin time is normal.

It should be stressed, however, that regardless of the diagnostic value accredited to either of the above in vitro tests, the two in vivo systems which they serve to demonstrate appear equally important and complementary in normal hemostasis.

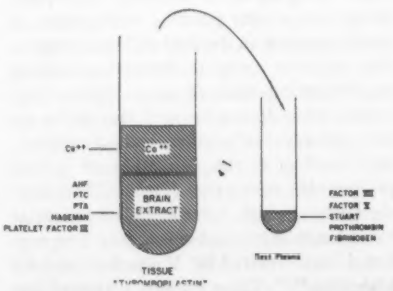

Fig. 3.—One-stage prothrombin time. To 0.1 ml. of test plasma are added 0.2 ml. of a mixture of brain extract ("thromboplastin") and 0.025 M $CaCl_2$, and the clotting time is recorded. The brain extract may be added to the plasma before the final addition of calcium.

† It has been shown that Factor VII, although required in the extrinsic system, is not necessary for the formation of thromboplastin in the intrinsic system.

‡ The platelet factor contributing to the generation of intrinsic thromboplastin.

Clinical Diagnosis

The clinical history and physical examination are important, as recently stressed by Diggs.[50] Numerous primary hemorrhagic disorders, as well as other systemic diseases, may be confused with the hemophilioid states. Clues to the nature of many of these conditions can usually be readily elicited if the various disease processes are kept in mind.

A congenital bleeding tendency will be suggested by a history of unusual persistent or recurrent hemorrhage following minor bruises, cuts, or skin punctures—as by a hypodermic needle—or following tooth extractions or other surgical procedures. On the other hand, a congenital diathesis is unlikely in any patient who has undergone major surgery without excessive bleeding. It must also be remembered that patients frequently tend to exaggerate bleeding episodes, and, to establish the significance of such episodes, specific questioning in regard to such matters as the need for medical attention, transfusions, or hospitalization for past bleeding experiences may often be helpful.

Inquiry regarding recent exposure to chemicals or drug ingestion, as well as evidence of preceding infection, may bring out a significant allergic history. Not infrequently, even today, one will encounter a scorbutic patient whose bleeding tendency may initially present an enigma until the nutritional history is brought into proper focus. The ascorbic acid (vitamin C) requirements of human adults and the degree of ascorbic acid deprivation necessary to produce scurvy have recently received exhaustive study.[51] One of the many points brought out by this study was that there was no correlation between capillary fragility tests and the state of ascorbic acid depletion.

The presence of a sex-linked history of a defect which is transmitted by females and limited to males suggests hemophilia or Christmas disease (PTC deficiency), since these are the only hemorrhagic conditions transmitted in this manner. However, the absence of a familial bleeding tendency does not necessarily exclude the possibility of hereditary disease, for the abnormality may not be expressed for several generations or may be so mild as to go unnoticed. Hence, about 50% of patients with hemophilia or Christmas disease fail to present any evidence of a familial disorder.

While a familial history of easy bruising or bleeding tendency is common in the congenital hemophilioid states, such a history may also be elicited in other hemorrhagic disorders, as, for example, in hereditary hemorrhagic telangiectasia, in some of those vascular purpuras associated with disturbances of coagulation, and in some thrombocytopenic purpuras. Fortunately, however, these other conditions can often be readily

TABLE 3.—*Distinguishing Features Between the Congenital Hemophilioid and Purpuric States* *

	Hemophilioid States	Purpuras
Bleeding source	Usually small artery	Usually capillary
Lesion	Intramuscular and deep hematomata, hemarthroses in severe cases	Cutaneous and mucosal petechiae and/or ecchymoses
Preceding trauma	Frequent	Unusual
Clean venepuncture	No superficial ecchymoses but may occasionally get massive hemorrhage if firm pressure not immediately applied	Small superficial ecchymoses common around venepuncture site
Transmission	Sex-linked hereditary history in approximately 40% of cases	No sex-linked hereditary history.
Sex predominance	Rare in females	Commoner in females
Bleeding time	Normal	Prolonged
Clotting time	Often prolonged	Normal
Tourniquet test	Negative	Frequently positive

* Hemophilia and Christmas disease constitute over 95% of the congenital hemophilioid states.

eliminated on the basis of other obvious gross observations—the visible mucosal or cutaneous vascular dilatations and regional localization of the hemorrhages in the telangiectases and a history of spontaneous small-vessel hemorrhage (purpura) in the vascular and thrombocytopenic purpuras (Table 3).

Hemarthroses are a hallmark of severe cases of the hemophilioid group but are rarely encountered in the purpuras and, while petechiae and/or multiple superficial ecchymoses are the rule in the purpuras, they are exceedingly rare in the hemophilioid states. Patients with vascular purpura or with congenital Factor VII deficiency, however, may present features of both the purpuric and the hemophilioid states.

Close attention to the distribution and morphology of the hemorrhagic lesions may often be very helpful. For example, flat cutaneous ecchymoses distributed over the backs of the hands are sometimes seen in elderly persons and may be the manifestations of the degenerative tissue changes accompanying aging ("senile purpura"). Elevated linear petechiae with associated scratch marks suggest an allergic origin. Petechiae distributed over the buttocks, knees, and elbows, preceded by swollen, painful joints and other evidence of systemic involvement, such as fever, malaise, and abdominal colic with melena, are features of Schönlein-Henoch purpura. Petechiae over the lower legs, arms, and mucous membranes are usually seen in the thrombocytopenic purpuras. Generalized petechiae may be associated with hemorrhagic emboli, as seen in meningococcal septicemia.

The presence of multiple bleeding sites rather than a single source of hemorrhage is also significant. For example, a history of simultaneous bleeding from several mucosal, cutaneous, and/or visceral sites is obviously more ominous than a history of recurrent episodes of simple epistaxis, which can usually be attributed to some local vascular anomaly.

In jaundiced patients the bleeding resulting from impaired vitamin K absorption secondary to bile duct obstruction should be differentiated from that associated with intrinsic liver disease.

Acquired hemophilioid states due to circulating anticoagulants are seen following pregnancy [26] and associated with systemic lupus erythematosis [25] or other chronic disease, and in previously healthy elderly patients.[24,27] Circulating anticoagulants may also occur as a secondary phenomenon in

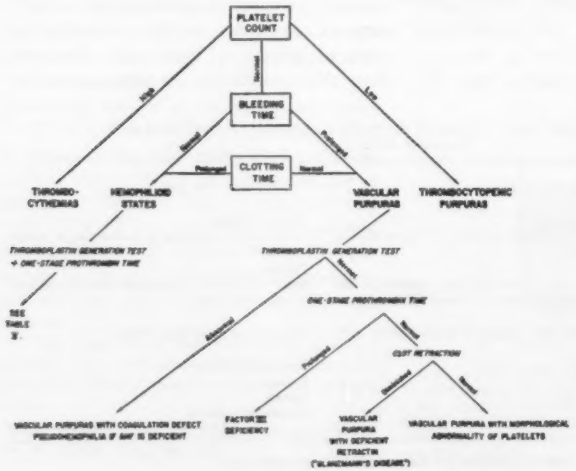

Fig. 4. — Diagnostic scheme for the hemorrhagic diatheses. The terminology of the vascular purpuras associated with a prolonged bleeding time, normal platelet count, normal AHF level, and normal clot retraction is confusing, and it is best in such cases to include briefly the pathological laboratory finding in the diagnosis. (See text.)

Christmas disease or in hemophilia.[23] This subject has been reviewed elsewhere by one of us.[22]

Unlike any of their hemophilioid counterparts, patients with Hageman-factor deficiency present no clinical manifestations of a bleeding tendency whatsoever, notwithstanding their in vitro coagulation defect.

Laboratory Diagnosis

By performing three simple screening procedures, i. e., a platelet count and the routine bleeding and clotting times, the *severer* bleeding disorders, previously outlined, can be readily classified (Fig. 4). Unfortunately, this scheme is of limited usefulness, since a normal clotting time is usually present in the *milder* hemophilioid states and a normal bleeding time may be obtained in certain instances in the *milder* purpuras. The congenital hemophilioid disorders may be further delineated by performing the one-stage prothrombin time and the thromboplastin-generation tests (Table 4).

Laboratory Methods

Bleeding Time.—The procedures described by Duke[52] or Ivy et al.[53] are both satisfactory. However, it should be realized that the bleeding time cannot be considered normal on the basis of a single result, and, in this instance, the procedure must be repeated several times at other cutaneous sites and at varying time intervals before considering the test negative.

Coagulation Time.—The use of two serology tubes is satisfactory. The vein must be entered immediately, and, after the first few milliliters of blood are withdrawn, the syringe is detached from the needle and 1 ml. of blood is allowed to flow directly into each tube, while a stop watch is simultaneously started. The tubes are immediately placed in a 37 C water bath and tilted at 30-second intervals until the first evidence of clot formation in each tube; the times are noted and averaged. This technique differs from the generally accepted procedure in

TABLE 4.—*Diagnosis of the Congenital Hemophilioid States*

Hemophilioid State	One-Stage Prothrombin Time	Deficient Fraction In TGT *	Differential Criteria †
Normal	Normal	None	
Hemophilia (AHF deficiency)	Normal	Adsorbed plasma	Sex-linked familial history
PTC deficiency	Normal	Serum	Sex-linked familial history
Hageman-factor deficiency PTA deficiency Circulating anticoagulant ‖	Normal ‡	Adsorbed plasma & serum §	Hemorrhagic episodes difficult to control with circulating anticoagulants, no bleeding with Hageman factor deficiency; test for circulating anticoagulants ‖
Platelet Factor 3 deficiency ("thromboasthenia")	Normal	Platelets	
Stuart-factor deficiency	Prolonged	Serum	
Factor V deficiency	Prolonged	Adsorbed plasma	
Factor VII deficiency Prothrombin deficiency Fibrinogen deficiency	Prolonged	None	Prolonged whole-blood clotting time with prothrombin deficiency only; fragile or absent whole-blood clot formation in severe fibrinogenopenia

* Thromboplastin generation test.

† In addition to specific cross matching studies.

‡ The circulating anticoagulants arising in patients previously normal in respect of blood coagulation and causing an acquired hemorrhagic diathesis may occasionally be associated with a prolonged one-stage prothrombin time. This is true of the circulating anticoagulants associated with lupus erythematosis ‖ and those circulating anticoagulants specifically directed against factors essential for the extrinsic system, e. g., circulating antifactor V ‖; in this case the thromboplastin-generation test result is also abnormal, since Factor V is also essential for the intrinsic system.

§ In both Hageman-factor deficiency and PTA deficiency, the thromboplastin generation is normal when either normal adsorbed plasma or serum are included in the incubation mixture, and an abnormal result is obtained only when the patient's plasma and serum are both utilized in the incubation mixture. In cases of low-titer anti-PTC or anti-AHF inhibitors either serum or adsorbed plasma, respectively, may be defective, but when the titer is considerable both serum and plasma are defective.

‖ Circulating anticoagulants are occasionally found as a secondary complication in hemophilia of Christmas disease (PTC deficiency) and are for this reason included in this Table. They are generally held to be antibodies specifically directed against AHF or PTC ‖.

that two instead of three tubes are used and both tubes tilted at regular intervals; this modification is believed by us to give more consistent results.

Platelet Count.—Any one of the recognized standard methods is satisfactory; we use the Brecher-Cronkite direct method.[54]

Thromboplastin-Generation Test.—The original method (Biggs and Douglas[55]) has been found by us to give excellent results. But this technique may be considerably simplified without loss of accuracy by certain modifications. Thus, uncoated instead of silicone-coated glassware may be used, and this serves to remove an important source of error frequently encountered by beginners (the use of improperly silicone-coated glassware). Samples from the incubating mixture may be conveniently taken at two-minute intervals rather than at one-minute intervals. Finally, if a platelet defect is not suspected, a cephalin extract, prepared by chloroform treatment of brain, may be used instead of platelets.[56]

One-Stage Prothrombin Time.—Excellent and reproducible results may be obtained by following the instructions of Quick.[49] We have found, however, that certain modifications are equally satisfactory if the same careful attention to detail is given (e. g., human-brain thromboplastin may be substituted for rabbit-brain thromboplastin).

Comment: The differential specificity of the intrinsic and extrinsic thromboplastin systems, as shown in Figure 1, provides a convenient scheme (Table 4) for the identification of the congenital hemophilioid states. In addition, this scheme may be employed to determine deficiencies of single coagulation factors encountered in certain purpuric states.

Multiple clotting-factor deficiencies have not been considered, but it should be noted that such conditions do exist in certain rare cases of congenital "purpuras," viz., vascular purpura with associated concomitant deficiencies of AHF and Platelet Factor 3.[57] Moreover, multiple deficiencies of clotting factors are the rule in acquired disturbances of clotting (e. g., liver disease and bishydroxycoumarin therapy), in which there are usually associated deficiencies of prothrombin, Factor VII, Stuart factor, and PTC—the so-called "prothrombin complex."

The proposed diagnostic scheme fails in those conditions where more than one coagulation factor is deficient. However, since congenital deficiency of prothrombin alone is exceedingly rare (only two reported cases have thus far satisfied the modern criteria for this diagnosis), it is readily apparent that a deficiency of prothrombin implies an acquired hemorrhagic condition in which Factor VII, Stuart factor, and PTC are also diminished. It is for this reason important to exclude a deficiency of prothrombin, and such a deficiency is excluded if the one-stage prothrombin time is less than one second above that of the normal control. However, should the one-stage prothrombin time be two seconds or more above normal, then more specific tests for prothrombin measurement must be resorted to. In such instances the prothrombin may be measured by a modification of the classical Iowa two-stage method, such as that of Wagner et al.,[58] or by a simple extension of the thromboplastin-generation test. It has been shown that when plasma deficient in one or more thromboplastin components is used as a test substrate in the thromboplastin-generation test instead of normal plasma, normal clotting times are obtained in all instances, provided normal reagents are present in the incubating thromboplastin mixture; the substrate clotting time in the presence of normal intrinsic thromboplastin is therefore a function of the substrate prothrombin and fibrinogen concentrations.[13,59,60] As a firm clot will not form when there is significant fibrinogenopenia, a simple prolongation of the clotting time resulting eventually in a firm clot will, under the above conditions, indicate a prothrombin deficiency, whereas a normal clotting time in such a system will exclude this possibility.

Other Laboratory Tests

Although not considered under the present diagnostic scheme, ancillary studies, such

as hemoglobin, white cell differential count with particular regard to platelet morphology, routine blood cell counts, capillary fragility, and clot-retraction studies should, of course, be performed routinely in the work-up of any patient presenting with an obscure hemorrhagic tendency.

In addition to the one-stage prothrombin time and the thromboplastin-generation test, the partial thromboplastin time (PTT) of Langdell et al.[61] is a most useful and rapid screening procedure for coagulation-factor deficiencies. This test is similar to the one-stage prothrombin time, but cephalin extract is used instead of brain. Although time-saving and simple in principle, considerable experience and careful attention to detail are essential to obtain reproducible results.[62] Recently a new two-stage screening test [63] has been described, in which samples of an incubating mixture of test plasma, buffer diluent, cephalin, and calcium are removed at intervals and added together with calcium chloride to a normal plasma substrate. Both the partial thromboplastin time and the new screening test are as sensitive, although not as specific, as the thromboplastin-generation test; a normal result in either test excludes a thromboplastin-component deficiency, with the exception of a Platelet Factor 3 deficiency.‖ Thus, if either one of these screening procedures indicates a clotting defect or if a qualitative platelet deficiency is suspected, it is still necessary to perform the thromboplastin-generation test to detect the specific abnormality. However, either test may be modified to give more specific results by determining whether the abnormality is corrected by normal serum or adsorbed plasma and may be substituted for the thromboplastin-generation test in the absence of a suspected platelet defect. Thus where a serum or plasma factor is defective in the thromboplastin-generation test, normal serum or adsorbed plasma, respectively, will correct the abnormal partial thromboplastin time [61,62] or new screening test. In Factor VII deficiency the partial thromboplastin time, the new screening test, and the thromboplastin-generation test will all be normal.

Tests of prothrombin utilization or consumption are still popular, but they only rarely give information that cannot be obtained by screening tests for thromboplastin generation or by the thromboplastin-generation test itself. Prothrombin consumption is often normal in many cases of mild hemophilia and Christmas disease (congenital PTC deficiency), and consumption tests are in general less sensitive than the thromboplastin-generation screening tests.[64] If consumption tests are used, they should therefore always be used in conjunction with a thromboplastin-generation screening test and not as substitute for this type of test.

It is to be stressed that absolute diagnosis of a hemophilioid state can be made only by cross matching the patient's plasma or serum with that of a patient with a proven congenital deficiency of the factor under test. But cross matching has limitations; it cannot be performed in the presence of a circulating anticoagulant and may give misleading information if the samples are stored in either the frozen or the lyophilized state because of deterioration of Factor V and possibly other factors. Moreover, blood from a patient with a proven congenital deficiency, with the exception of hemophilia, is rare, and samples usually have to be mailed to a coagulation research center. However, the provisional diagnosis arrived at by use of the routine procedures outlined in the above scheme will almost always be correct, except in the very rare instance where the patient lacks a hitherto undescribed coagulation factor.

Treatment

The treatment of all the hemophilioid states is in principle the same and may best be considered in two phases: (1) the urgent attention required for active severe bleeding, whether internal or external, and (2) the judicious conservative management nec-

‖ The screening tests for thromboplastin generation do not reflect a deficiency of Platelet Factor 3, since a platelet substitute, cephalin, is added to the test plasma.

essary during the quiescent intervals of the disease or in the case of minor hemorrhages.

In any instance of severe, unremittent hemorrhage, transfusions of either fresh or stored whole blood, as the need may be, are necessary as an emergency measure. Such transfusions serve not only to restore the concentration of circulating hemoglobin and replace lost fluid but also as a source of the deficient coagulation factor or factors. They thus promote hemostasis and serve ultimately to terminate the vicious cycle of hemorrhage and the associated perpetual depletion of residual coagulation factors. The type and amount of fluid required in any particular case will depend upon a number of factors—the duration and severity of the bleeding, the hemoglobin concentration, the weight of the patient, and the degree and nature of the particular clotting-factor deficiency. In hemophilia the levels of AHF range from 0% in the severe cases to approximately 30% in the milder cases [65,66]; hence the hemostatic level of AHF must be above the latter figure. In order to increase the antihemophilic activity 1%, approximately 1 ml. of fresh normal plasma per kilogram of body weight must be given,[64,67] but it is to be stressed that this figure is merely an average one, since the concentration of AHF in fresh bank blood is extremely variable. It has been shown that the in vivo half-life of AHF ranges from 4 to 11 hours [67,69] and the in vitro (stored bank blood) half-life may range from less than 12 hours [46] to 2 weeks.[68] In calculating the amount of AHF required, it is also important to bear in mind that distribution of AHF between vascular and extravascular compartments occurs.[70] Usually at least 1,500 ml. of whole blood, or its plasma equivalent, less than 24 hours old will be required over a 24-hour period to effect hemostasis in the milder adult cases. It is exceedingly difficult to achieve a hemostatic level in a severe hemophiliac, and very large amounts of plasma or whole blood may be required. The clinician will be guided in any case mainly by the course of the bleeding and should strive to effect its control with whatever amount of blood or plasma is deemed necessary. It will usually be found most efficacious to prime the patient with a loading dose of at least 1 liter of whole blood (or its plasma equivalent, if the hemoglobin concentration is satisfactory) over as short a period as appears safe, in an attempt to achieve adequate hemostatic levels of the required coagulation factor, and then to follow this dosage with slower—drip—maintenance infusions.[64,67] Purified AHF extracts of bovine, pig, and human blood have been used experimentally with very promising results [71-74]; an average dose of 200 to 400 mg. of the bovine material is equivalent in activity to about 2,500 ml. of fresh human plasma.[73] These materials should be administered intravenously, although there is now evidence that AHF may be absorbed by the intramuscular route.[70] Unfortunately, owing to the potential antigenicity of animal products, their use must at present be restricted to extreme emergencies only.

PTC appears to be considerably more stable in routinely stored bank blood than AHF, and the in vivo half-life of PTC is probably longer than that of AHF. It is therefore easier to achieve a hemostatic effect with transfusions in Christmas disease.[75] While the critical hemostatic level of AHF appears to be roughly 35%,[46] the critical level of PTC is not known, and so clinical judgment must to a large extent determine the volume of blood or plasma to be infused in cases of Christmas disease. Probably 1 liter of plasma over a 24-hour period will suffice in even the severest case.¶

As both Christmas disease and hemophilia may be complicated by the appearance or presence of circulating anticoagulants,

¶ A recent experience of one of us (C. H.), in which over 2 liters of plasma given over a period of 24 hours failed to achieve a hemostatic level in a moderately severe case of Christmas disease, suggests that considerably larger doses of plasma may be required in this condition.

this fact should be borne in mind, for it is very difficult, if not impossible, to achieve a hemostatic effect in most of these cases by transfusion of blood or plasma.[22]

Routinely stored bank blood or plasma, not more than 7 days old,# may be used in all of the hemophilioid states with the exception of hemophilia, Factor V deficiency, and Platelet Factor 3 deficiency. However, transfusions are rarely required in the treatment of deficiencies of Factor V, Factor VII, PTA, or the Stuart factor. Whenever large amounts of stored blood or plasma are administered to any patient, the risk of thrombocytopenic purpura should be constantly borne in mind.[76]

In general, elective surgery is contraindicated in all the hemophilioid states (with the exception of Hageman-factor deficiency). Conservative management is the rule except in cases of dire emergencies when surgery cannot possibly be avoided. In such instances a hemostatic level of the deficient factor should be obtained prior to the surgical intervention. Unless this is done feeble clots will form in the ligated bleeding vessels while the level of any particular coagulation factor is low, and with the postoperative absorption of the ligatures hemorrhage will most certainly ensue.[73] A similar problem is posed in the management of dental extractions in these patients, and here again the administration of plasma *just before* the extractions is indicated, and multiple tooth extractions at one sitting should be avoided.[77]

Minor hemorrhages from cuts and abrasions may usually be controlled by the local application of thrombin or Russell viper venom. Hemarthroses should be handled conservatively by keeping the patient comfortably at rest and applying a backsplint to the involved joint. The usual analgesics may be given for associated pain. Needling of the joint is advised by many authorities, but our experience with this measure is, in general, unfavorable, and we cannot recommend it; usually the joint swelling will subside in a few days without any treatment.

While mild cases of any of the hemophilioid states who do not give a history of hemarthroses should not be discouraged from participating in active sports, those who have suffered from hemarthroses should definitely be restricted in their athletic activities. Last but not least, psychotherapy, with emphasis on reassurance, plays a very important role in the management of these patients.

The general principles in the management of the acquired hemophilioid states are similar to those outlined above. However, vitamin K should be given in all cases in which the hemorrhagic manifestations are associated with a prolongation of the one-stage prothrombin time due to any of the following three causes: excessive dosage of the coumarin drugs; failure of absorption of vitamin K from the intestine, as in idiopathic steatorrhea or obstructive jaundice, and deficient stores of vitamin K, as in hemorrhagic disease of the newborn. Phytonadione (vitamin K_1) is superior to the synthetic water-soluble compounds in counteracting excessive dosage of the coumarin drugs.

In cases of "fibrinolytic purpura," fibrinogen or whole blood transfusion is usually recommended.[31] The treatment of the thrombocytopenic states and pseudohemophilia has been recently well reviewed by Harrington [30] and Buchanan and Leavell,[38] respectively, and is outside the scope of the present review.

Summary

The diagnosis and treatment of the hemophilioid states have been reviewed in the light of recent investigations. Confusion in this field has been fostered by a multiple and rather chaotic nomenclature of both the various clinical entities and the coagulation

John B. Graham (personal communication) has shown that aged plasma which may be several weeks old is as effective as fresh plasma in achieving a hemostatic level in Christmas disease. This is probably also true in cases of Factor VII and Stuart factor deficiencies, but this has not yet been established.

factors, and a few suggestions have been proposed to help enhance our understanding of these conditions.

The primary hemorrhagic diatheses fall into three etiologic groups: (1) the congenital and acquired hemophilioid states, (2) the vascular purpuras, and (3) the thrombocytogenic purpuras. The importance of the routine clinical history and physical examination in the diagnosis of these conditions is stressed.

In many instances, a bleeding tendency may be readily classified into one of the above categories on the basis of three simple laboratory determinations: a platelet count and bleeding and clotting times. Discussion of the practical application of present-day theories of blood coagulation to clinical practice has revealed the importance of two additional routine laboratory procedures—the one-stage prothrombin time and the thromboplastin-generation test—in further identifying the hemophilioid states. It is hoped that the proposed simplified diagnostic scheme will serve in some measure as a guide for today's busy practitioner and perhaps stimulate a more intensive and enlightened investigation of these disorders as they are encountered in everyday practice.

The place of blood and plasma transfusions, as well as a more conservative approach in the management of the hemophilioid states, is discussed.

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Unrecognized Myocardial Infarction

A Clinicopathologic Study

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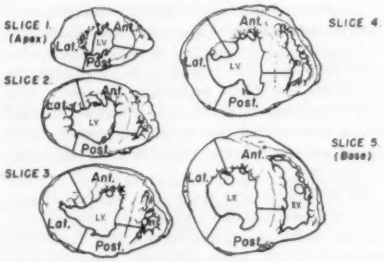
Although myocardial infarction has become increasingly well recognized, there continue to appear at necropsy myocardial infarcts, especially healed ones, which had been unrecognized clinically. It is also apparent that these unrecognized infarcts represent a considerable proportion of the myocardial infarcts at necropsy.[1] It was therefore felt worth while to study the case histories and the necropsy data on patients with myocardial infarction in order to determine the incidence of clinical nonrecognition and attempt to clarify some of the factors that obscured the diagnosis.

Methods

Cases for study were selected from the necropsies performed at the Mayo Clinic during the years 1953 and 1954. To be included in this study the case had to meet three prerequisites: (1) The medical record had to be apparently adequate with respect to the past history, physical examination, and details of the symptoms at the onset of the final illness; (2) the heart had to present pathologic evidence of either a healed or an acute infarct measuring 2 cm. in at least one dimension, and (3) the predominant lesion had to be one of coronary disease.

Each heart was examined grossly in the manner described by Achor and co-workers,[1] that is, the ventricles were sliced into five serial sections transverse to the long axis of the heart. In the localization of the infarcts the left ventricle was considered to be divided into three portions by the anterior and posterior papillary muscles and an imaginary line dividing the anterior two-thirds of the ventricular septum from the posterior one-third. These portions were designated anterior, posterior, and lateral (Figure). Infarcts involving predominantly the endocardial half of the left ventricle were termed "subendocardial," while those involving all or almost all of the entire thickness of the ventricular wall were classified as "transmural." In some instances the infarct was represented by a conglomerate mass of scar tissue or necrotic myocardium, while in others normal muscle was interspersed with small patches of myocardial necrosis or fibrosis. For further subdivision, the former lesions were designated as "conglomerate" and the latter, "patchy" infarcts.



Localization of infarcts.

Sections taken from representative areas of gross infarction were studied microscopically in order to verify the presence of myocardial infarction and to provide an estimate of the histologic age of the infarct according to the criteria of Mallory and co-workers.[2] Infarcts estimated to be 4 weeks old or older were designated as "healed," and those estimated to be less than 4 weeks old were termed "acute."

In the review of the histories a search was made for a record of angina pectoris, congestive heart failure, hypertension, diabetes mellitus, or any previous history suggesting prolonged coronary in-

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sufficiency or myocardial infarction. After each history was reviewed a decision was made as to whether or not myocardial infarction had been diagnosed or suspected at any time prior to the patient's death. Mention of "coronary occlusion," "acute coronary insufficiency," or "acute myocardial infarction" in the final clinical note made after the patient's death was not accepted as a clinical diagnosis unless at least some suspicion had been indicated in previous clinical notes.

In those patients with acute myocardial infarction the time of onset was estimated on the basis of symptoms, laboratory data, electrocardiograms when present, and histologic age of the infarct. The circumstances at the onset of the acute attack were noted with particular reference as to whether the patient was ambulatory or bedfast, whether he was being seen primarily for cardiac or noncardiac complaints, and whether any surgical procedures were carried out immediately before or after the onset of the attack.

The clinical patterns at the onset of acute infarction were identified and classified as follows: (1) cases in which pain generally accepted as characteristic of cardiac origin occurred at the onset of the attack; (2) cases in which typical cardiac pain was lacking and in which the predominant manifestations were shock, pulmonary edema, or congestive heart failure; (3) cases in which there were atypical symptoms, such as abdominal complaints, symptoms referable to the central nervous system, or disturbances of cardiac conduction, and (4) asymptomatic cases in which even in retrospect there were no symptoms that could be attributed to cardiac infarction.

In patients with acute infarcts all of the electrocardiograms were reviewed, and the electrocardiographic evidence was classified as "not diagnostic," "suggestive," or "diagnostic." Situations wherein electrocardiograms were taken previous to onset of the attack and not afterward were considered as "not done." Most of the patients for whom electrocardiograms were recorded had three standard, three unipolar extremity, and six precordial leads, but in some cases only three standard and three precordial leads were recorded.

Results

Cases Selected for Study.—We selected 143 cases of either acute or healed myocardial infarction or both for study out of a total of 1,267 necropsies performed during the years 1953 and 1954. These cases represented 11.3% of the total necropsies. Of the 143 patients, 105 (73%) were men and 38 (27%) were women. However, of the entire necropsy population, 789 were men (62%) and 478 were women (38%). Therefore, the 105 men represented 13.3% of all necropsies performed on men, while the 38 women represented 7.9% of all necropsies performed on women; thus, on the basis of these percentages the ratio of men to women with myocardial infarction was less than 2:1. The average age at the time of death was 68 years for the women and 66 years for the men. In 80 (56%) of the 143 cases healed infarcts alone were found; in 33 (23%) both healed and acute infarcts were found, and in 30 (21%) acute infarcts alone were found. Thus, 63 patients had acute infarcts, and 113 patients had healed infarcts, patients having both types of infarcts being counted in each category.

Incidence of Antemortem Recognition of Myocardial Infarction.—Of the 113 patients with healed infarcts, only 49 (43%) had a positive diagnosis during life. In 8 other patients (7%) infarction was suspected, but in 56 patients (50%) there was no record of a clinical diagnosis or suspicion of myocardial infarction (Table 1).

TABLE 1.—*Factors Related to Clinical Recognition or Nonrecognition of Healed Myocardial Infarcts*

	Patients with Healed Infarcts				
	Diagnosed		Not Diagnosed		
Factor	No.	%*	No.	%*	Total
Angina pectoris	48	53	10	17	58
Congestive heart failure	20	61	13	39	33
Hypertension	27	52	25	48	52
Diabetes mellitus	12	52	11	48	23
All cases	57	50	56	50	113

* % of corresponding number in last column.

Of 63 patients with acute myocardial infarcts, 30 (47%) had a positive diagnosis during life. In 8 patients (13%) acute infarction was suspected, but in 25 (40%) this diagnosis was not made or suspected prior to death. Therefore, in this series the infarction was unrecognized clinically in 50% of the patients with healed infarcts and in 40% of those with acute infarcts.

Factors Related to Clinical Nonrecognition of Healed Infarcts.—The records of the 113 patients with healed infarcts varied considerably in the comprehensiveness of the histories, particularly with respect to the past history. Therefore, each of the histories was classified as being "fair," "good," or "excellent." In 24% of the series the histories were "fair," in that the patients were interviewed by at least two physicians and their records included a past history and a review of systems. However, the majority of such patients were seen only for their final illness, which in many cases was unrelated to their coronary disease. In addition, some of these patients did not give good histories, were partially deaf, or were at times confused. In 43% of the series the histories were "good." These patients were seen several times, usually at yearly intervals, for the last few years of their life. In 33% the histories were "excellent." The majority of these patients were local residents or cardiac patients who were seen frequently and had undergone extensive investigations including repeated electrocardiographic examinations.

As would be anticipated, a history of angina pectoris or of previous myocardial infarction was elicited most frequently when the histories were "excellent" and least frequently when they were only "fair." Thus, of the 37 patients with "excellent" histories, 22 (59%) had a history of angina pectoris and 20 (54%) had a diagnosis of previous infarction. Twenty-seven (55%) of the forty-nine patients with "good" histories had a history of angina pectoris or previous infarction, and only nine (33%) of the twenty-seven patients with "fair" histories had such a history. This suggests that the availability of the patients for repeated questioning increased the proportion from whom a history of precordial pain was obtained. Nevertheless, the fact remains that of the 37 patients questioned repeatedly over many years, there were 15 (41%) in whom no history of angina pectoris was obtained, although at necropsy they had severe coronary sclerosis with healed myocardial infarcts.

The most important factor leading to a correct diagnosis of previous myocardial infarction was a history of angina or of an episode of prolonged substernal pain suggestive of myocardial ischemia. As shown in Table 1, in 48 (83%) of the 58 patients who had a record of angina pectoris a correct diagnosis of infarction had been made or suscepted during life. To a less extent a history of previous congestive heart failure also favored recognition of previous infarction, since 20 (61%) of the 33 patients with such a history were correctly recognized clinically to have had myocardial infarction. Of the 13 patients who had previous congestive heart failure but unrecognized infarcts, 9 had hypertension, 2 had chronic auricular fibrillation, 1 had senile dilatation of the aorta with a murmur of aortic insufficiency, and 1 had severe pulmonary emphysema. Thus, none of these patients had clinically unexplained conges-

TABLE 2.—*Type and Principal Location of 126 Healed Infarcts* *

Type & Principal Location	Healed Infarcts					
	Recognized		Unrecognized		Total	
	No.	% †	No.	% †	No.	% of Respective Totals
Subendocardial						
Anterior & anterolateral	13	54	11	46	24	40
Lateral	4	33	8	67	12	20
Posterior & posterolateral	4	27	11	73	15	25
C-shaped or circumferential	6	67	3	33	9	15
Total	27	45	33	55	60	100
Transmural						
Anterior & anterolateral	15	68	7	32	22	33
Lateral	4	36	7	64	11	17
Posterior & posterolateral	21	64	12	36	33	50
Total	40	61	26	39	66	100
Patchy	30	48	33	52	63	50 ‡
Conglomerate	37	59	26	41	63	50 ‡

* Of the 113 patients with healed infarcts, 101 had single healed infarcts and 12 had multiple healed infarcts.
† % of corresponding number in column headed "Total."
‡ % of 126.

tive heart failure. The presence of hypertension or diabetes mellitus, on the other hand, did not appear to have a significant effect on the incidence of recognition of previous infarction.

Whether healed infarcts had been recognized during life bore some relationship to their location (Table 2). Of the subendocardial infarcts, the lateral and posterior scars were less often recognized than the anterior and the "C-shaped," * or circumferential, ones. In regard to transmural infarcts, the lateral ones were less often recognized than those in the anterior and posterior locations. In general, subendocardial infarcts were less frequently recognized (45%) than were the transmural ones (61%). While the relationship between distribution of the infarcts (that is, whether patchy or conglomerate) and incidence of recognition was not striking, conglomerate infarcts were diagnosed more frequently by 11%.

Factors Related to Clinical Nonrecognition of Acute Infarction in Patients Dying with Acute Myocardial Infarction.—At the time of necropsy, 63 patients had demonstrable acute myocardial infarcts; 42 (67%) of these were men, and 21 (33%) were women. This ratio of men to women was approximately the same for patients having recognized acute infarction as for patients having unrecognized acute infarction. However, in the latter group both sexes averaged four years older than they did in the former. Thus, it seemed that while the sex of the patient had no bearing on the ease of diagnosis, older patients were more commonly represented among those having unrecognized acute infarction.

The fact that an infarction had occurred previously did not in itself appear either to facilitate or to interfere with diagnosis of a subsequent one. If a previous infarction had been recognized, there was a slightly greater tendency to be aware of a recent one, but if a previous infarction had been overlooked, the subsequent one was very likely to be unrecognized also. Nine persons had both old and recent myocardial infarcts that were unrecognized. None of these patients had a history of angina or of substernal pain at the estimated time of infarction, and only two had electrocardiograms. All of these patients had some mental clouding during their final illness. A previous history of angina pectoris facilitated the diagnosis of recent infarction, since 80% of the patients with recognized infarction had such a history, as compared with 44% in the group with unrecognized infarction. A previous history of congestive heart failure, hypertension, and diabetes was approximately equally common in the two groups and thus did not appear to have a significant bearing on the ease of diagnosis.

Data on the predominant symptoms at the onset of acute infarction in these 63 patients are presented in Table 3. A majority of patients having clinically recognized infarction had typical thoracic pain (77%), and the remainder had manifestations either of heart failure (10%) or of upper abdominal distress (13%). On the other hand, only one-third of the patients with unrecognized infarction had thoracic pain; one-fourth had symptoms of heart failure, and one-third had no record of symptoms that could be attributed to infarction. In the eight patients who had typical substernal

TABLE 3.—*Symptoms at Onset of Acute Myocardial Infarction*

	Patients with Acute Infarcts					
	Diagnosed		Not Diagnosed		Total	
Symptom	No.	% of 38	No.	% of 25	No.	% of 63
Thoracic pain	29	77	8	32	37	58
Dyspnea	2	5	1	4	3	5
Congestive heart failure	2	5	5	20	7	11
Atypical symptoms	5	13	3	12	8	13
Asymptomatic	0	0	8	32	8	13
Total	38	100	25	100	63	100

* A "C-shaped" infarct is one involving the subendocardial portion of the anterior wall, septum, and posterior wall of the left ventricle.

pain and yet did not have a correct diagnosis there were a variety of reasons for nonrecognition. In four patients the pain of acute infarction was mistaken for an episode of angina pectoris; in two others it was interpreted as thoracic wall pain, and in one it was ascribed to an existing pulmonary carcinoma; one additional patient had a stroke immediately before admission to the hospital and was unable to tell the hospital physician about the thoracic pain that had preceded the hemiplegia, although this history had been communicated to the physician who saw her at home. None of the 63 patients had shock or syncope alone as the presenting manifestation. Only three patients had acute dyspnea alone as the predominant complaint, and in two of these the myocardial infarction was readily diagnosed. Thus acute dyspnea did not seem to be an important factor in obscuring the diagnosis of acute infarction, since it occurred frequently in patients complaining of substernal constricting pain and infrequently in those without pain.

At the onset of the acute attack a majority (74%) of patients with recognized infarction were active at home at the time of infarction and came to their physician with a cardiac complaint. When the infarction occurred in the hospital or during the course of investigation or treatment of noncardiac complaints, it was more likely to be overlooked. This was especially true of surgical patients, particularly during the postoperative period. Sixteen patients underwent some surgical procedure during their final hospitalization. Three were patients who had undergone diagnostic instrumentation, and in two of these endoscopic examination may have precipitated infarction; the remaining patient had a healing infarct, and instrumentation preceded sudden death. Six patients were operated upon during recovery from acute infarction, and each died within four days after operation. Seven patients experienced myocardial infarction postoperatively. Five of these occurred within the first 4 days after operation, and the other two came on after 11 and 20 days, respectiveiy. In only one of the five patients who sustained acute myocardial infarction during the immediate postoperative period was the correct diagnosis established clinically.

The electrocardiograms were diagnostic or suggestive in two-thirds of the 30 patients with diagnosed infarction (Table 4).

TABLE 4.—*Electrocardiographic Observations in Acute Myocardial Infarction in Sixty-Three Patients*

	Clinical Category					
	Diagnosed		Suspected		Not Diagnosed	
Electrocardiogram	No.	% of 30	No.	% of 8	No.	% of 25
"Not done" *	2	7	1	13	13	52
Not diagnostic	8	27	4	49	6	24
Suggestive	1	3	2	25	6	24
Diagnostic	19	63	1	13	0	0
Total	30	100	8	100	25	100

* Electrocardiograms recorded before the onset of acute infarction and not repeated later were classified as "not done."

They were not diagnostic in eight patients (27%), and electrocardiographic examination was not done in two (7%). The electrocardiograms were not helpful in one-half of the group of patients suspected of having acute infarction. In the one patient with an electrocardiogram diagnostic of acute myocardial infarction in this group cardiac arrest developed after bronchoscopic examination, but the patient recovered temporarily after prolonged cardiac massage. The electrocardiographic changes recorded during the week that this patient survived were erroneously presumed to have been due to myocardial trauma from the massage. Of the 25 patients having undiagnosed acute infarction, 13 (52%) did not have electrocardiograms and 6 (24%) had nondiagnostic electrocardiograms. Of the six patients in this group with suggestive changes, two were interpreted as having old infarcts and the remainder as having left ventricular strain or showing digitalis effect. The distribution of the acute infarcts

TABLE 5.—*Type and Principal Location of Sixty-Four Acute Myocardial Infarcts**

Type & Principal Location	Infarcts		
	Recognized	Unrecognized	Total
Subendocardial			
Anterior	4	7	11
Lateral	0	0	0
Posterior	1	4	5
Circumferential	1	0	1
Total	6	11	17
Transmural			
Anterior	11	6	17
Lateral	1	2	3
Posterior	18	6	24
Circumferential	3	0	3
Total	33	14	47
Patchy	8	11	19
Conglomerate	31	14	45

* Of the 63 patients with acute myocardial infarction, 1 had 2 acute infarcts.

according to type, location, and clinical recognition or nonrecognition is given in Table 5. The numbers in each category are too small to be of much statistical value, but it appears that patchy subendocardial infarcts, particularly those limited to the posterior wall, were more often unrecognized than the conglomerate transmural ones.

In Table 6, patients who had typical cardiac pain are compared with those who had no history of thoracic pain at the estimated time of acute infarction. Almost all patients (92%) experiencing characteristic cardiac pain had a previous history of angina pectoris. This was in contrast to the small number (27%) with an anginal history among the group with painless infarction. There was only slight difference in the average per cent of cardiac hypertrophy between the "painful" and "painless" groups, and this may be explained by the slightly higher incidence of hypertension and congestive heart failure in the "painless" group. Almost one-half of the patients without typical thoracic pain had some clouding of consciousness during their final illness. Although disease of the gallbladder was common in both groups of patients, it did not seem to be an important factor in obscuring the symptoms, except in four patients who had predominant abdominal complaints at the time of their myocardial infarction. Previous infarction occurred more frequently in patients without typical thoracic pain, being present in 69% of those without pain and in 41% of the ones with retrosternal pain. Acute coronary thrombosis was found in 46% of the patients with acute myocardial infarction, and in the majority of these instances (89%) it resulted in transmural infarction. The incidence of acute thrombosis in the group with cardiac pain was identical with that in the group without pain, although the incidence of transmural infarction was slightly higher in the group with typical cardiac pain.

The records of the 25 patients who had unrecognized acute myocardial infarction

TABLE 6.—*Correlation of Pain as a Symptom of Acute Infarction with Other Pertinent Clinical and Pathologic Data*

	Symptom at Onset of Acute Infarction					
	Typical Cardiac Pain (37 Patients)		Other Symptoms or Asymptomatic (26 Patients)		Entire Series (63 Patients)	
	No.	% of 37	No.	% of 26	No.	% of 63
Previous angina	34	92	7	27	41	65
Previous hypertension	21	57	18	69	39	62
Previous congestive heart failure	7	19	7	27	14	22
Impaired sensorium	4	11	12	46	16	25
Chronic cholecystitis with stones	8	22	7	27	15	24
Previous infarction	15	41	18	69	33	52
Acute coronary thrombosis	17	46	12	46	29	46
Transmural infarction	28	76	18	69	46	73
Subendocardial infarction	9	24	8	31	17	27
Average % of cardiac hypertrophy	—	65	—	75	—	70

TABLE 7.—*Incidence of Clinical Recognition of Pathologically Proved Myocardial Infarction*

Period of Study	Author	Age of Infarct	Total Cases	Correctly Diagnosed		Remarks
				No.	%	
1927-1936	Bean[3]	Acute	176	114	65	
1941-1946	Yater and coworkers[4]	Acute	203	116	57	Men 18-39; sudden deaths not included
1946-1950	Achor and coworkers[1]	Healed	227	108	48	
1953-1954	Johnson and coworkers	Acute	62	38	61	Sudden deaths not included
		Healed	113	57	50	
1954-1955	Paton[5]	Acute	170	118	69	Included sudden deaths in hospital patients

were reappraised. In retrospect, four of these infarctions should have been diagnosed, since the histories were suggestive of acute infarction and the electrocardiograms were compatible with this diagnosis but had been misinterpreted as indicative of "left ventricular strain" or "previous infarction." Five patients had histories suggestive of acute infarction but had inadequate electrocardiographic studies. In all of these nine cases the clinical diagnosis could probably have been established had sufficient electrocardiograms been recorded. Four other patients experienced infarction postoperatively but did not have complaints sufficiently suggestive of cardiac disease to prompt electrocardiographic investigation. Three additional patients were operated upon during the healing phase of an acute infarction. One of these was a man with known coronary disease who had a history typical of gallbladder colic and was cleared for surgical treatment without a preoperative electrocardiogram. The other two patients had no history suggestive of coronary heart disease. The remaining nine patients had had other diseases that obscured the diagnosis. Three were admitted with cerebral infarction, and one had an occlusion of the mesenteric artery. Two were admitted with congestive heart failure attributed erroneously to aortic stenosis in one case and aortic insufficiency in the other. In the remaining three patients mental confusion or the multiplicity of the patient's complaints obscured the diagnosis.

Comment

A number of clinicopathologic studies deal with the incidence of unrecognized myocardial infarction, some of which are listed in Table 7. Since the cases in these studies were selected in different ways, the figures listed are not strictly comparable. The series of Yater and co-workers[4] included young men 18 to 39 years of age from whom adequate histories were obtained. A group of 247 cases was not included because sudden death prevented adequate investigation. Despite this careful selection, only 57% of the acute myocardial infarctions were recognized clinically. The study by Achor and co-workers[1] and the present one were done at the same institution, and similar criteria were used in selecting the cases. In both studies only one-half of the patients with proved healed infarcts had a clinical history of previous myocardial infarction. In the present study only 60% of the acute infarctions were recognized or suspected clinically. Paton[5] included sudden deaths in his series. Of the patients with proved acute infarcts, 69% were recognized. However, an additional 96 patients had a clinical diagnosis of acute infarction that was proved incorrect at necropsy. If these errors in diagnosis are included as well as those instances in which pathologically proved acute myocardial infarction was overlooked, the clinical diagnosis was correct in only 44% of the cases.

The figures collected from different investigators over a span of 20 years certainly indicate that despite advances in electrocar-

diography the clinical diagnosis of myocardial infarction continues to be surprisingly inaccurate. On the other hand, the electrocardiographic diagnosis, particularly if repeated 12-lead electrocardiograms are recorded, has been reported to be 80% accurate.[6] If the single set of tracings does not show changes suggestive of myocardial damage, usually no further follow-up tracings may be taken. Thus, in the present series of cases lack of suspicion resulted in failure to obtain any electrocardiograms in one-quarter of the patients with necropsy-proved acute myocardial infarction. Of the 47 patients in whom at least one electrocardiogram was obtained, 20 (43%) had unequivocal evidence and 9 (19%) suggestive evidence of myocardial infarction. In the remaining 18 patients (38%), few of whom had serial studies, the electrocardiograms were not diagnostic of acute myocardial infarction.

The main reason for failure to suspect the presence of myocardial infarction was absence of characteristic thoracic pain during the attack or lack of a previous history of angina pectoris. Even though congestive heart failure developed in one-fourth of these patients with unrecognized myocardial infarction, the infarction was not suspected when thoracic pain was absent. This attitude undoubtedly has been fostered by many clinical studies in recent years which have stressed the low incidence of painless myocardial infarction.[7] It is true that most patients with acute infarction have some thoracic pain, but in an appreciable number pain is neither severe nor prolonged and is easily overlooked and often forgotten by the patient. Occasionally when the patient is having repeated attacks of anginal pain it is difficult to know which attack represents the onset of myocardial infarction.

One of the major factors obscuring the pain of fatal acute myocardial infarction is the clouding of consciousness that so often accompanies these attacks.[8] This blunting of the patient's awareness of pain may result from a variety of disturbances. It may be due directly to concomitant cerebral infarction associated with acute myocardial infarction, or it may be related to impairment of the cerebral circulation as a result of diminished cardiac output following myocardial infarction.[8,9] Hypotension following severe hemorrhage, operation, or spinal anesthesia may cause cerebral circulation as well as coronary blood flow to be insufficient. Narcotics given for postoperative pain during the first few days of convalescence may also mask cardiac pain.[10] In addition, fatal myocardial infarction may occur during the course of some systemic disease in which cerebral function is impaired because of uremia, diabetic coma, or other metabolic disturbance.

Summary

One hundred forty-three cases in which the presence of acute or healed myocardial infarcts or both was established at necropsy performed at the Mayo Clinic during the two-year period 1953 and 1954 were studied. In 57 (50%) of 113 patients with healed infarcts the condition had been clinically diagnosed or suspected. In 56 patients (50%) there was no clinical diagnosis or recorded suspicion of previous myocardial infarction. Of 63 patients who died during acute myocardial infarction, 38 (60%) had a correct clinical diagnosis and 25 (40%) did not.

The most important factor in the failure to recognize healed or acute infarcts was the absence of angina pectoris or of a history of prolonged thoracic pain. Such a history was obtained almost twice as frequently in patients with healed infarcts who were seen repeatedly as in patients who were seen only for their terminal illness. However, even among the group of patients who were seen repeatedly, there was an appreciable number (41%) who had no history of angina pectoris or of previous acute substernal pain, even though severe coronary atherosclerosis and gross myocardial scars were present at necropsy.

The coexistence of acute dyspnea, congestive heart failure, hypertension, or dia-

betes mellitus did not appear to influence greatly the incidence of correct antemortem diagnosis. The average age of patients with undiagnosed acute infarction was four years greater than that of patients with recognized infarction, but the sex distribution was the same in the two groups.

With both acute and healed myocardial infarcts, correct antemortem recognition was somewhat more frequent when the lesions were conglomerate and transmural in extent rather than patchy and subendocardial. Among the transmural infarcts those located laterally were more often unrecognized, while among the subendocardial infarcts those situated laterally and posteriorly were more difficult to diagnose. These differences in frequency of recognition were unrelated to the incidence of pain and were probably related to the increased likelihood of obtaining electrocardiographic confirmation when myocardial infarction occurs anteriorly.

In 20 of 47 patients with acute myocardial infarction who had electrocardiograms taken after the estimated onset of the infarction the electrocardiographic evidence for acute infarction was unequivocal, and in 9 it was suggestive. Thus, in 29 of 47 instances (62%) the electrocardiogram gave supportive evidence of myocardial infarction. These results probably reflect an insufficient number of follow-up electrocardiograms in patients whose symptoms did not strongly suggest myocardial infarction and are not a good index of the diagnostic accuracy of the electrocardiogram.

A history of characteristic thoracic pain was often absent when infarction occurred in the immediate postoperative period, was accompanied by shock, occurred in patients who had concomitant strokes or sudden occlusion of other major arteries, and occurred in patients whose state of consciousness was altered by other systemic diseases.

Mayo Clinic.

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Pulmonary Infections Complicating Asian Influenza

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Asian influenza was first noted in New Haven late in September, 1957, and during the ensuing month a large number of patients with influenza was seen at the New Haven Hospital. In most the illness was benign; however, 91 were hospitalized during a six-week period in October and early November for a complication of influenza, usually pneumonia. Eleven of these patients died. It is the purpose of this report to summarize the experience with the complications of influenza, with particular emphasis on fatal cases of pneumonia.

Epidemiology

The arrival of the epidemic in New Haven was heralded by a sudden sharp increment in the number of adult medical patients seen in the emergency clinic. Usually medical house officers see from 120 to 150 patients per week, of whom only 10% have complaints referable to the respiratory system. This relationship is depicted in Figure 1 (Weeks 1-4). On Oct. 3, 1957, the number of patients with respiratory illness increased sharply, and it reached a peak during the last two weeks in October (Weeks 7 and 8), when 170 and 157 were seen. The number of emergency-clinic visits for nonrespiratory illnesses remained relatively constant, and the group with influenza represented a new patient population. The epidemic ended as abruptly as it had begun, and by the second week in November (Week 10) emergency-room traffic had returned to normal.

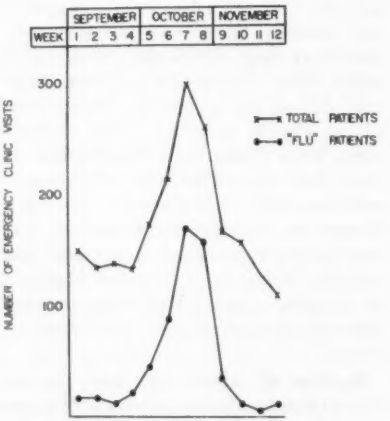

Fig. 1.—Number of adults seen in the emergency clinic during the influenza epidemic of 1957.

The large influx of patients with complaints of fever, malaise, cough, and chest pain necessitated the establishment of criteria for admission to the hospital or treatment on an outpatient basis. All patients were examined carefully, and those with severe cough, positive findings on examination of the chest, or an elevation of temperature greater than 104 F had chest x-rays taken. Leukocyte counts were also made, and those patients found to have values higher than 15,000 WBC per cubic millimeter were also screened for pulmonary infiltrates. Particular care was taken to avoid confusion with serious bacterial in-

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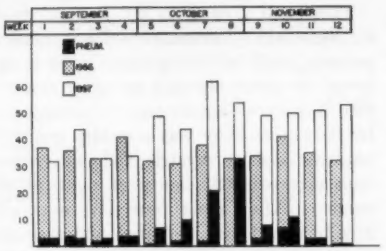

Fig. 2.—Number of patients admitted to University Medical Service of the Grace-New Haven Community Hospital during September, October, and November, 1957, and the corresponding period in 1956.

fections, e. g., meningococcal meningitis or streptococcal tonsillitis.

The large majority of patients could safely be permitted to return to their homes for care; only those with pulmonary infiltrates were admitted to the hospital. No serious errors in diagnosis are known to have been made with use of this screening technique, and only an occasional patient returned because symptoms failed to improve on symptomatic therapy.

Nevertheless, 91 patients with pneumonia were hospitalized during the six-week period beginning in October, 1957. This represented a sixfold increase over the same period in 1956 and a marked increment over the patients with pneumonia admitted during September, a nonepidemic period (Fig. 2). At the peak of the epidemic, in late October (Weeks 7 and 8), 54 patients with pneumonia were admitted to the hospital. The outbreak subsided rapidly, and within two weeks after the crest admissions for pneumonia had fallen to normal levels (Weeks 11 and 12, Fig. 2).

Clinical Features of Postinfluenza Pneumonia

On clinical and epidemiological grounds most of the 91 patients admitted to the hospital during the six-week period in October and November were assumed to have postinfluenza pneumonia, and these cases form the basis of this study.

Sex, Age, Race.—Fifty-three patients were males and thirty-eight females. Among the males, 19 were under 40 years of age and 26 were older than 50. On the other hand, 24 of the 38 females were between the ages of 16 and 40. These figures suggest that old men were prone to develop pneumonia following influenza and that females were most vulnerable during the child-bearing period. Of special interest in regard to the latter possibility is the fact that 10 of the 24 were pregnant, about three to four times the expected incidence. Negroes appeared to be more susceptible to pulmonary infections following influenza than members of the white races, since 40 of 91 patients were Negroes, whereas only about 15% of medical ward patients at the New Haven Hospital are Negroes.

Etiology of Pneumonia.—At the time of admission, bacteriologic studies included culture of sputum and blood and Gram-stain of the sputum. These laboratory studies revealed that 38 patients had bacterial pneumonia. Diplococcus pneumoniae was the etiologic agent in 24 patients, 3 of whom had bacteremia. Hemolytic Staphylococcus (Micrococcus) pyogenes var. aureus was implicated in six patients, two of whom had the organism isolated from blood cultures, and Hemophilus influenzae was the predominant organism in six instances. One man had a lung abscess which had developed in an untreated pneumonia and which contained several species of bacteria, and Proteus vulgaris was cultured from the sputum of a patient who had been treated with chlortetracycline prior to entry (Table 1, Group I).

TABLE 1.—*The Etiology of Postinfluenza Pneumonia*

Bacterial (Group I)		38
D. pneumoniae	24(3)*	
H. influenzae	6	
S. pyogenes var. aureus	6(2)*	
P. vulgaris	1	
Mixed	1	
Etiology undetermined (Group II)		43
Acute tracheobronchitis (Group III)		10

* Patients with bacteremia.

The sputum of 43 patients, in whom pulmonary infiltrates were demonstrated by x-ray or at autopsy, showed no predominant organism with Gram-stain and grew only "normal mouth flora" on culture. These patients were designated as having pneumonias of undetermined etiology (Table 1, Group II).

Finally, 10 patients were thought to have pneumonia after initial readings of chest x-rays. Review of the dry films, however, demonstrated only an increase in bronchial markings. These patients have been classified as acute tracheobronchitis (Table 1, Group III). From a clinical and bacteriologic point of view, they in no way differed from those in Group II.

It was not practicable to attempt to demonstrate influenza-virus infection in every one of the 91 cases. Blood for hemagglutination inhibition tests and throat washings for virus cultures were obtained in a number of instances to show that such an infection had been present. For example, six of seven patients in Group I and seven of seven patients in Group II had at least a fourfold rise in hemagglutinin-inhibition titers. Two additional patients had the virus isolated from throat washings, and in three fatal cases it was recovered from the lungs at autopsy. These findings, when added to the epidemiologic data presented above, make it appear almost certain that the Asian-influenza virus was a factor in the pathogenesis of the majority of these infections.

TABLE 2.—*Symptoms of Ninety-One Patients with Postinfluenza Pulmonary Infection*

Symptom	Group * I Bacterial (38)	II Etiology Undetermined (43)	III Tracheobronchitis (10)
Antecedent influenza	26	24	2
Cough	34	40	10
Sputum	29	30	4
Pleuritic pain	15	13	3
Rigors	21	7	2

* No. patients in each group given in parentheses.

Signs and Symptoms of Patients with Postinfluenza Pneumonia.—Two clinical patterns could be distinguished in these patients. In about one-half an upper respiratory illness preceded the onset of pneumonia. In such cases there was a sudden onset of headache, malaise, myalgia, and chilly sensations approximately one week prior to admission. After about four days a cough, usually productive, appeared and was associated with a further rise in temperature. In the remaining cases symptoms of pulmonary involvement appeared concomitantly with headache, muscle pain, and fever. Pleuritic pain occurred in one-third of patients. Shaking chills were seen in 21 of 38 patients with bacterial pneumonia (pneumococcal, 18; staphylococcal, 2; H. influenzae, 1), whereas only 9 of the remaining 53 patients had rigors. With the exception of the last parameter, the clinical picture of patients with bacterial pneumonia was similar to that seen in the group with nonspecific bacteriologic findings (Table 2).

Ninety per cent of patients had temperature elevations to 101 F or higher, and in many the temperature ranged between 104 and 106 F. The highest temperatures were observed in the patients with bacterial pneumonia. The duration of pyrexia varied widely, but in most instances fever persisted for at least 48 to 72 hours after admission (Table 3).

Special attention was given to the appearance of the sputum. Grossly bloody sputum came to be regarded as a grave prognostic sign, and all five patients who expectorated large quantities of frankly bloody sputum died. Three had staphylococcal pneumonia, and two had an overwhelming pneumonia of uncertain etiology. Blood-streaked or rusty

TABLE 3.—*Highest Temperatures Observed in Postinfluenza Pulmonary Infections*

	Group I (38)	II (43)	III (10)
<101	5	4	0
101–104	22	31	9
>104	11	8	1

TABLE 4.—*Appearance of Sputum*

	Group		
	I (38)	II (43)	III (10)
Mucoid	4	11	2
Blood-streaked	12	9	1
Bloody	3	2	0
Purulent	10	7	1
Insignificant amounts	9	14	6

sputum was common, but its presence did not imply a poor prognosis. Purulent sputum was commonest in patients with pneumococcal pneumonia. Nearly one-third of all patients had no significant sputum production (Table 4). In this regard, aspiration of the trachea with a sterile catheter, which resulted in a cough productive of bronchial secretions, was often helpful in obtaining sputum for diagnostic study. This maneuver was successful in three patients critically ill with staphylococcal pneumonia in whom prompt appropriate treatment was mandatory.

It became clear, as the epidemic progressed, that leukopenia was also an ominous prognostic sign. Five of six patients whose white blood cell counts were less than 5,000 died. These patients had 600, 800, 3,500, 4,400, and 4,500 WBC per cubic millimeter, with an absolute granulocytopenia (Table 5). Bone marrow aspirations in two showed leukemoid arrest. The only person with leukopenia who recovered was a man with multiple myeloma and splenomegaly, who had a chronically depressed leukocyte count. Twenty-nine patients had normal total leukocyte counts, and included in this group are eight who were regarded as having bacterial pneumonia. However, all of them exhibited a relative increase in granulocytes. The highest leukocyte counts were observed in some patients with bacterial pneumonia.

TABLE 5.—*Leukocyte Counts*

	Group		
	I (38)	II (43)	III (10)
<5,000	3	3	0
5–10,000	8	15	6
10–15,000	7	16	4
>15,000	20	9	0

Underlying Abnormal Physiological or Pathological States.—Undoubtedly patients with chronic illnesses are more likely to seek medical attention for upper respiratory infections than are persons previously in good health. Nevertheless, the evidence is highly suggestive that patients with pregnancy, heart disease, or chronic lung disease were especially susceptible to postinfluenza pulmonary infections (Table 6). There were 10 pregnant women in this group, all but 1 in the last trimester or at term. Four were delivered of healthy infants while on the medical service. Eleven patients had heart disease: four, rheumatic; one, congenital with right-to-left shunt; three, coronary artery, and three, hypertensive. The high incidence of acute pneumonia in patients with chronic pulmonary insufficiency is well known; this was corroborated by the presence of 14 patients with chronic bronchitis, pulmonary fibrosis, and emphysema in this series. Five patients with cerebral arteriosclerosis and four diabetics were admitted with pneumonia during the period of study. Only a few chronic alcoholics presented with pneumonia. This is in contrast with a nonepidemic period, when the majority of patients admitted to this hospital with pneumonia are chronic alcoholics. Other diseases associated with this epidemic of pneumonia were lupus erythematosus, multiple myeloma, sicklemia, cerebral palsy, and chronic renal insufficiency. Only 36 of all patients

TABLE 6.—*Underlying Diseases in Patients with Postinfluenza Pulmonary Infection*

	Group			
	I (38)	II (43)	III (10)	Total
Pregnancy	4	4	2	10
Heart disease	2	7	2	11
Chronic pulmonary disease	8	5	1	14
Cerebral arteriosclerosis	4	1	0	5
Diabetes mellitus	0	3	1	4
Chronic alcoholism	3	0	0	3
Other	3	4	1	8
None	14	19	3	36

were without complicating disease or pregnancy.

Results of Treatment

All patients who had bacterial pneumonia by smear and culture of the sputum received antibiotic therapy. Patients with pneumococcal infection were given penicillin; those with H. influenzae infection received streptomycin and chloramphenicol; staphylococcal pneumonia was treated with massive doses of penicillin (20,000,000-100,000,000 units per day), streptomycin, and erythromycin, and/or chloramphenicol. Seven patients died and will be discussed in detail. One patient developed a lung abscess, and two had sterile pleural effusions which eventually cleared.

No bacterial agent was indicted as a cause for the pneumonias in the patients in Group II. In spite of this, the majority were treated with antibiotics, usually penicillin alone or in combination with streptomycin, because despite negative cultural findings it was felt that bacterial infection may have played a role, particularly in patients with lobar consolidation, leukocytosis, purulent sputum, or chronic pulmonary disease. Eighty per cent of these patients responded promptly to antimicrobial therapy, and, though it may be argued that improvement would have occurred spontaneously, there were several instances where antibiotics had been withheld for 48 to 72 hours and prompt improvement in clinical state and defervescence occurred after penicillin therapy had been instituted. On the other hand, it must be acknowledged that 12 patients in Group II and 7 in the tracheobronchitis category recovered promptly without the aid of antimicrobials. This suggests that some of these infections were solely of viral etiology.

In these groups (II and III) there were four deaths, and in three patients resolution was prolonged but recovery was complete (Table 7).

TABLE 7.—*Results of Therapy*

	Group		
	I (38)	II (43)	III (10)
Chemotherapy	38	31	3
Improvement	28	24	3
Slow resolution	3	3	0
Death	7	4	0
No chemotherapy	0	12	7
Improvement		12	7

Fatal Cases of Postinfluenza Pneumonia

During this six-week period of study, 11 of 91 patients admitted to the hospital for pneumonia died. Four of them were old and debilitated, with serious chronic disease.

One, a 72-year-old man, was admitted in coma and with a temperature of 94 F. He died within 24 hours of admission, and autopsy disclosed staphylococcal bronchopneumonia involving all lobes. A second man, aged 76, was addicted to alcohol and was admitted with acute pancreatitis. Sputum culture yielded H. influenzae. He was treated with chloramphenicol and streptomycin but died on the seventh hospital day. At autopsy focal areas of pneumonia were found in both lungs. Two other patients, 68 and 77 years of age, had severe hypertensive heart disease and generalized arteriosclerosis. Both had severe pneumonia clinically and by x-ray, and at autopsy one patient had a severe necrotizing pneumonia and S. pyogenes var. aureus was cultured from the lungs, while the other manifested little evidence of pneumonia and the findings were consistent with protracted congestive heart failure.

These four patients were suffering from potentially lethal chronic diseases. However, it is clear that the pulmonary infection which they contracted during the influenza epidemic played an important role in their demise.

The remaining seven deaths involved young previously healthy adults who suddenly succumbed to an overwhelming infection characterized by an abrupt onset, high fever, marked toxicity, severe dyspnea, bloody sputum, leukopenia, and finally anoxia and circulatory failure. The pertinent clinical findings are summarized in Table 8 and in the brief abstracts which follow.

TABLE 8.—*Clinical Features of Fatal Postinfluenza Pneumonia* *

Age	Sex	Bacteriology	Sputum	Bl. Cult.	Lung	WBC	Virus Isol.
19	M	S. pyogenes var. aureus	Bloody	+	R, L	800	+
39	F	S. pyogenes var. aureus	Bloody	—	R, L	4,500	+
52	F	S. pyogenes var. aureus	Bloody	+	R	3,800	ND
43	M	No bacteria	Bloody	—	R, L	4,400	—
14	M	No bacteria	?	ND	R, L	12,000	+
14	M	ND	Bloody	—	R, L	600	ND
62	M	D. pneumoniae	Purulent	+	R	15,000	ND

* + indicates positive; —, negative; ND, not done.

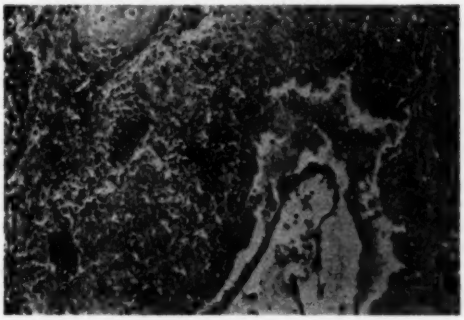

Fig. 3.—Section through wall of bronchus, showing denudation of epithelial lining and necrosis of wall.

A 19-year-old college student was well until five days before admission, when he developed symptoms typical of influenza. Four days later he was admitted to the college infirmary because of cough. On the following day he developed a temperature of 106 F, became cyanotic, and was referred to the hospital. Although he was severely dyspneic and cyanotic, physical examination revealed only a few rales over the right posterior chest. X-ray examination, however, showed extensive bilateral pneumonia. Aspiration of the trachea yielded bloody material loaded with Gram-positive cocci, which on culture proved to be S. pyogenes var. aureus, sensitive to many antibiotics, including penicillin. The leukocyte count was 800 per cubic millimeter, and the bone marrow showed leukemoid arrest. The patient was treated with penicillin, 20,000,000 to 100,000,000 units per day, as well as erythromycin, 4 gm. per day, and was also given hydrocortisone, but he died 48 hours after entry.

At postmortem examination both lungs were red, edematous, and twice the normal weight. Microscopic examination showed necrotizing tracheobronchitis, severe hemorrhagic pneumonia with necrosis, hyaline-membrane formation, and abscesses. Myriads of staphylococci were visible in all sections (Figs. 3 and 4). These organisms, with antibiotic sensitivity unchanged, were cultured

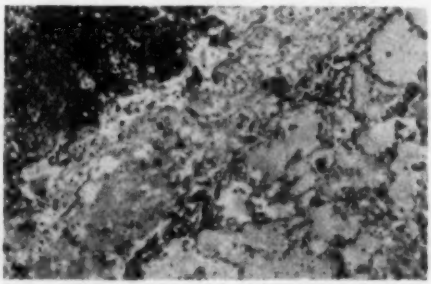

Fig. 4.—Lung with hemorrhage (upper left) and extensive edema.

from the lung at autopsy. Asian-influenza virus was also isolated from his lung tissue.

A 39-year-old woman, in the sixth month of pregnancy, developed a cough, malaise, and slight fever three days before admission. She received penicillin and tetracycline wihout relief of symptoms and because of a feeling of tightness in her chest was admitted to the hospital. Shortly after entry active labor began, and she was delivered of a dead fetus. After delivery her temperature was 102 F and a few rales were detected in the chest, but x-ray examination was not performed. During the next 12 hours, however, dyspnea and cyanosis developed rapidly, and she became hypotensive and died 15 hours after delivery. Prior to death aspiration of the trachea yielded bloody sputum loaded with staphylococci, and treatment with penicillin and erythromycin had been instituted.

Autopsy revealed hemorrhagic, edmatous lungs, and only the extreme apices presented a normal gross appearance. Histologic study showed extensive necrosis and hemorrhage, as well as microabscess formation. S. pyogenes var. aureus and Asian-influenza virus were isolated from the lungs.

A 43-year-old man had had a left upper lobectomy for pulmonary tuberculosis three years previously but had been well and able to work. Six days prior to admission he developed symptoms of a mild upper respiratory infection. On the day before entry he became severely dyspneic and cyanotic. Examination disclosed signs of consolidation in the left lung, and x-ray showed scattered infiltrates throughout that organ. Although the sputum was bloody, no pathogenic micro-organisms were found on repeated cultures. The pneumonia spread to his right lung, and in spite of vigorous treatment with massive doses of penicillin, chloramphenicol, streptomycin, and isoniazid he died six days after entry.

Postmortem findings were similar to those described above. Tracheitis was not pronounced, but there was marked accumulation of edema fluid and fibrin in the alveoli, and hyaline membranes were prominent (Fig. 5). In this patient neither virus nor pathogenic bacteria were obtained from the lung.

A 14-year-old boy was admitted to the neurosurgical service because of generalized weakness, dysphagia, and dysarthria. These symptoms had appeared two days before and were associated with a temperature elevation of 102 F. Physical examination revealed weakness of all muscles as well as diminished function of the 9th, 10th, 11th, and 12th cranial nerves. The lungs were entirely clear. Lumbar puncture was normal on two occasions. He developed marked respiratory distress without significant cough or signs of pulmonary infiltration, and a mechanical respirator, as well as tracheostomy and treatment with penicillin and streptomycin, was employed. In spite of these measures, he died five days after admission.

At autopsy, the central nervous system showed no abnormalities grossly or microscopically. The lungs, however, were identical to those seen in lethal postinfluenza pneumonia. This impression was corroborated by the finding of Asian-influenza virus in the pulmonary tissue.

A 63-year-old Negro man was admitted in a moribund state. His family stated that he had been perfectly well until two days prior to entry, when he developed the "flu." On the morning of admission he was found unresponsive and was sent to the hospital. Examination showed him to be in shock, with a temperature of 103 F and signs of pneumonia in the right lung. He died within one hour. Cultures of blood and sputum yielded D. pneumoniae. At autopsy the findings were typical of pneumococcal pneumonia in various stages of progression. The left lung was entirely normal.

With the exception of the last, these patients presented with a uniform clinical picture. All had mild upper respiratory and systemic symptoms for several days, fol-

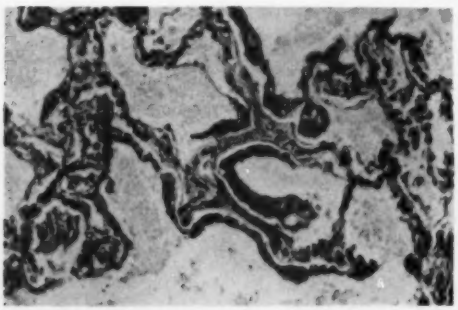

Fig. 5.—Alveoli lined with "hyaline membranes."

lowed by the sudden onset of dyspnea, cyanosis, cough, high fever, and systemic toxicity. Bloody sputum and leukopenia were present in all but two patients. Physical findings were scanty, although x-rays showed extensive infiltration. The course was steadily downhill, with increasing respiratory distress and a clinical picture resembling pulmonary edema. Anoxia appeared to be a serious problem and was not relieved by oxygen therapy. Terminally shock, unaffected by vasopressors or adrenal cortical hormones, supervened.

With the exception of the last case, the pathological picture was similar in all patients. Grossly, the lungs were heavy and hemorrhagic and looked more like liver than lung; microscopically, the salient features consisted of marked hemorrhage, edema, necrosis of alveolar tissue, the formation of hyaline membranes, and microabscesses. There appeared to be no difference between the cases in which Staphylococcus or viruses were demonstrated and those in which pathogens were absent.

Comment

In spite of the small number of cases subjected to virological analysis and proved to be associated with infection by Asian-influenza virus, it is reasonable to assume that the large majority of patients admitted to the hospital because of pneumonia during October and early November, 1957, developed the disease as a complication of influenza. The occurrence of epidemic influenza had been anticipated; nevertheless, the severity of the complicating pneumonias was somewhat surprising. All of the fatalities described here occurred between October 15 and 25, at a time when the incidence of influenza reached its peak in the community.

The large number of patients presenting themselves in the outpatient department posed the difficult problem of distinguishing between those whose illness was to run a benign course from those in whom a relatively mild upper respiratory infection would be transformed into a life-threatening pneumonia. It became evident early in the epidemic that patients with normal chest x-rays, or in whom the films showed only peribronchial infiltration, invariably did well no matter how ill they appeared. Although leukocyte counts were performed in all patients with the thought that leukocytosis would be an indicator of secondary bacterial infection, it became clear that the majority of severely ill patients had low, rather than high, white blood cell counts. Pyrexia could not be relied on as a prognostic or diagnostic sign, and a number of patients with comparatively little coughing had widespread pneumonia. Blood-streaked sputum, on the other hand, always connoted the presence of pulmonary infiltration, and grossly bloody sputum appeared to be a warning that massive destruction of pulmonary tissue was in process. It should be emphasized that physical examination of the chest frequently provided no clue that extensive pneumonia was present, and radiological examination was the only definitive method to rule out pulmonary infection. This was clearly illustrated by the patient, admitted to the hospital on another service with a diagnosis of "encephalitis," who was found to have severe pneumonia at necropsy not suspected clinically. Similar was the case of the pregnant woman admitted in labor, in whom the diagnosis of pneumonia was not made until a few hours before death.

Actually, fulminating pneumonia associated with influenza has been well described in the literature, both during the 1918-1919 pandemic [1] and the influenza-A epidemic of 1940-1941.[2] Chickering and Park described an illness which they designated S. pyogenes var. aureus pneumonia in an Army camp in 1918. Their patients, mostly young men, had typical influenza succeeded by a fulminating illness with cyanosis, anxiety, high fever, circulatory collapse, and death. Other clinical features of this illness, which closely resemble those seen in our patients, were scarcity of physical findings in the lungs, absence of herpes labialis, rarity of demonstrable bacteremia, leukopenia, poor prog-

nostic implication of hemorrhagic sputum, and relative rarity of suppurative complications, presumably because the disease ran its course before they could develop. Pathologically as well as clinically, the similarity between the cases described by Chickering and Park and those seen in the present epidemic was striking. In both instances the lungs were swollen and hemorrhagic, with multiple minute abscesses in various stages of development. Severe necrotizing tracheobronchitis was a prominent postmortem finding. Staphylococci were isolated from cultures of the lung in most cases. Winternitz et al. described a similar pathological picture in postinfluenza pneumonia studied during the 1919 epidemic.[3] However, in his group of patients a wide variety of organisms was cultured from the lungs.

Finland, Peterson, and Strauss reported the clinical and pathological findings in 66 cases of staphylococcal pneumonia which occurred in Boston during the 1940-1941 influenza epidemic.[2] Despite marked variation in pulmonary findings, rapidly fatal pneumonia occurred in seven, the clinical picture and necropsy findings resembling those described here.

It becomes obvious from these reports that the fulminant form of postinfluenza pneumonia is, in effect, an old acquaintance.[4] It is puzzling, however, that while in many epidemics of influenza the illness is remarkably uniform, the course, benign, and the case fatality, low, some outbreaks are associated with a significant incidence of lethal pneumonia.

Whether influenza virus or secondary bacterial infection is of primary etiologic importance in the pathogenesis of these pneumonias is not clarified by the present studies. Although the Asian strain of influenza virus was isolated from the lung in three cases, hemolytic staphylococci were found in two of these. On the other hand, one of three patients whose lungs were sterile at autopsy had no demonstrable influenza virus. Another in whom virological examination gave negative results showed many staphylococci in the lungs. In spite of these inconsistencies in etiologic findings, the pathologic picture, consisting of an acute tracheobronchitis with diffuse involvement of the pulmonary parenchyma, necrosis of the alveoli, hyaline-membrane formation, and relatively acellular hemorrhagic exudate, was remarkably uniform, not only in our patients but in others elsewhere in the United States[5] and England.[6] In some fatal cases viruses were isolated from lungs which were bacteriologically sterile, and in others many different species of bacteria were cultured. Similar observations were made during the 1918-1919 pandemic, in which a great variety of bacterial species was associated with different outbreaks. Winternitz clearly demonstrated the wide spectrum of postmortem bacteriology when he described 14 distinct organisms recovered from 34 cases of pneumonia manifesting relatively uniform lesions anatomically.[3]

The presence of virus in pulmonary tissue does not indicate conclusively that it is responsible for the pneumonia, particularly at a time when air-borne dissemination must be high. However, when this finding is considered in conjunction with the uniform clinical and pathologic picture which has been found in the presence of a highly diversified bacterial flora, the conclusion that the virus per se is responsible for initiating the large majority of these infections becomes difficult to deny. While it is true that invasion by bacteria produced much destruction of pulmonary tissue, there is much to suggest that the pathologic picture seen in lethal postinfluenza pneumonia may occur in the absence of micro-organisms. This concept gains support in the observation that antimicrobial therapy was unsuccessful in some cases despite the fact that the bacterial flora of the sputum (S. pyogenes var. aureus in most cases) was sensitive in vitro to the antibiotics employed. Stuart-Harris has noted that the outcome in fatal cases of postinfluenza pneumonia has not been affected appreciably by chemotherapy,[7] and this has been confirmed in several outbreaks during the 1957 epidemic.[5,8]

There is little doubt, however, that antibacterial chemotherapy was of value in achieving a cure in some patients with bacterial pneumonia, particularly when caused by the pneumococcus. Perhaps failure of antibiotics in the fatal cases can be ascribed to the finding that death seemed to be related more to severe anoxia and reduced cardiac output resulting in peripheral vascular collapse than to overwhelming infection. The clinical picture of "pulmonary edema" rather than lobar pneumonia was borne out to some extent at the autopsy table. Therefore, the question arises whether therapeutic procedures usually employed in treatment of acute left ventricular failure, such as use of digitalis, mercurial diuretics, oxygen by positive pressure, and phlebotomy, might have been helpful. Adrenal cortical hormones, used primarily for their anti-inflammatory action, appeared to have no effect. "Exhaustion" of the adrenal glands did not occur, and the organs appeared normal at autopsy.

Despite these speculations, the massive involvement of both lungs with necrosis and edema renders unlikely the possibility that any therapeutic maneuvers other than the host's natural defenses could have reversed the process. Perhaps support of the patient's vital functions might be provided by means of an extracorporeal heart-lung pump, allowing sufficient time for natural defense mechanisms to come into play. The subject warrants further study.

Although the emphasis in this report has been placed on 11 patients, it should be pointed out that they represented the only fatal cases associated with influenza in a community of 200,000 in which many thousands must have had the disease. Why these patients contracted this lethal form of pneumonia remains an enigma. The evidence is suggestive, however, that pregnant women, patients with rheumatic heart disease, and those with chronic pulmonary insufficiency are particularly susceptible to the development of pulmonary infections associated with influenza. Vaccination against influenza virus would seem to be of special importance in these groups. It should be noted that none of the 91 patients included in this study had been vaccinated against Asian influenza.

A preventive approach necessitates consideration of the administration of prophylactic antibiotics either at the time symptoms of influenza first appear or even upon contact of the pneumonia-prone patient with a person ill with influenza. Since antibacterial prophylaxis is of proven value only when employed against a single organism, such as meningococcus, Streptococcus, or Neisseria gonorrhoeae (gonococcus), it would not be expected to be effective in protecting against infection with one or several of the bacteria usually found in association with influenza.[9] The bacterial complications of measles have not been favorably affected by the use of prophylactic antibiotics; indeed, the secondary invaders in such patients have been more difficult to eradicate.[10]

There is every reason to believe that the latter observations are applicable to influenza and that routine prophylactic antimicrobials would result only in the development of more resistant secondary infections and a higher incidence of sensitization to these drugs. Certainly administration of antibiotics did not prevent the appearance of pneumonia in many patients in the present study. Efforts to prevent the viral infection by immunization seems a more rational approach to prophylaxis.

Summary

During the Asian-influenza epidemic in October, 1957, ninety-one patients with pulmonary infections associated with influenza were admitted to the New Haven Hospital. Of these, 38 had bacterial pneumonias, 24 of which were due to Diplococcus pneumoniae; 6, to Staphylococcus pyogenes var. aureus, and 6, to Hemophilus influenzae. In 43 patients with pulmonary infiltrates no specific pathogenic bacteria seemed to be present. Ten patients manifested only severe tracheobronchitis.

In about one-half of the cases symptoms of typical influenza preceded the appearance of pneumonia, while in the remainder the illness began with symptoms attributable to pulmonary infection. Cough and fever were present in almost all patients, while pleuritic pain and rigors were seen primarily in those with bacterial pneumonia. Bloody sputum was present in five fatal cases and was an ominous prognostic sign, as was leukopenia.

Pregnant women and patients with heart and chronic pulmonary disease seemed to be unusually susceptible to postinfluenza pneumonia.

Antimicrobial therapy in 28 of 38 patients with bacterial pneumonia resulted in defervescence within 72 hours. Twenty-four of forty-three patients with pneumonia of undetermined etiology also improved rapidly on antibiotics. A number in this group, however, did well in the absence of chemotherapy.

Eleven patients died; four were old people with serious chronic disease, but seven were previously healthy adults who had a fulminating illness characterized by severe toxicity, bloody sputum, high fever, leukopenia, anoxia, and circulatory failure. Antibiotics, adrenal cortical hormones, and other supportive measures were ineffective. Autopsy in these patients revealed a hemorrhagic necrotizing pneumonia, and staphylococci and influenza virus were isolated from the lungs of three patients. The uniformity of the clinical and pathologic picture in this group suggests that the virus is the primary etiologic agent in pneumonia associated with influenza.

Dr. Robert H. Green performed virus isolations from throat washings and hemagglutinin inhibition tests, and Dr. Lisbeth M. Kraft performed virus studies on autopsy specimens.

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Case Reports

Spontaneous Hypoglycemia Associated with Massive Hepatoma

A Review of Current Concepts and Report of a Case

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The first report of primary carcinoma of the liver associated with hypoglycemia was a case described by Nadler and Wolfer, in 1929.[1] The authors considered that the hypoglycemia could have resulted at least in part from a quantitative loss of liver substance, but they were disturbed by the absence of symptoms suggestive of hepatic insufficiency. Relatively little has been added to clarify this problem since the initial publication. This can be partially explained by the paucity of reports of hypoglycemia associated with hepatoma. Although primary carcinoma of the liver is an uncommon tumor in this country, it is, nevertheless, estimated to occur in 0.47% of autopsied cases.[2] However, there have been only five reports relating this tumor to hypoglycemia.[1,3-6] It is of interest that no mention is made of hepatoma as a cause of hypoglycemia in the extensive review of the causes of hypoglycemia by Conn * and Seltzer.[7] So poorly is the mechanism of the hypoglycemia understood, there are at least as many as and possibly more theories than there are cases reported. However, in 1956, McFadzean and Yeuny [6] studied 23 consecutive cases of hepatoma in Chinese males and found that hypoglycemia occurred in 7. They concluded that hypoglycemia resulted because the liver tumor avidly utilizes all exogenous glucose, thus diverting it away from peripheral use. The following report is a case of massive hepatoma associated with spontaneous hypoglycemic coma and a discussion of the possible physiopathologic mechanisms involved.

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* Dr. Jerome Conn stated in a personal communication that he believes hepatomas associated with hypoglycemia should be classified with other nonpancreatic tumors which because of massive size and avid utilization of glucose cause hypoglycemia.

Report of Case

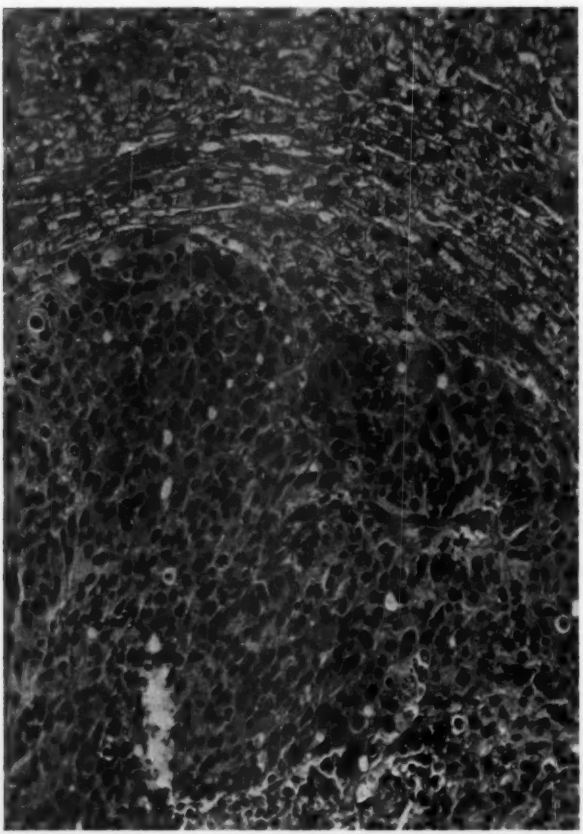
A 62-year-old white woman was brought to Mt. Carmel Mercy Hospital in a comatose state, responding only to painful stimuli. Relatives stated that she had been anorexic and had lost 15 lb. during the preceding 15 months. There had been a progressive loss of strength and periodic episodes of tremulousness relieved by drinking milk. On the morning of this hospitalization she "awoke but was unable to move out of bed." She was brought to the hospital several hours later, at which time she was almost completely unresponsive. On physical examination her skin was pallid and moist. Funduscopic examination was normal. The extremities were flaccid, with equal tendon reflexes. Blood pressure was normotensive. Lungs were clear. There was a soft apical systolic murmur but no other cardiac abnormalities. The abdomen appeared distended, and a large firm irregular mass was palpated, filling both upper quadrants and extending down below the right iliac crest. The remainder of the examination was negative. Blood cell counts were not remarkable except for a mild hypochromic anemia. Urinalysis was moderately positive for acetone. Blood sugar and nonprotein nitrogen samples were sent to the laboratory, and, until more definitive studies could be outlined, an intravenous infusion of 500 cc. 5% dextrose in water was started. Shortly thereafter, the intern noted, "the patient is fully awake and oriented to time, place, and person." Subsequently, the blood sugar value was reported as less than 30 mg. %. The patient

remained alert following the intravenous dextrose infusion and was able to take nourishment orally. Subsequently a chest x-ray revealed a rounded opacity in the right lung base and a similar lesion in the left lung field, reported as apparently metastatic nodules. A barium swallow revealed marked irregular enlargement of the liver, displacing the stomach to the left. Skull x-rays were normal. An ECG was abnormal in that there were low-voltage T-waves in the standard limb leads, aV_R, aV_L, and aV_F, and V_4 through V_6. The following blood chemistries were done on the second hospital day; Na, 139 mEq. per liter; K, 2.9 mEq. per liter; Cl, 570 mg. %; CO_2-combining power, 68 vol. %; alkaline phosphatase, 4.7 Bodansky units; total protein, 7.4 gm.; albumin, 3.5 gm. %; globulin, 3.9 gm. %; bilirubin, direct, 0.4 mg. %, and total, 0.9 mg. %; cholesterol, 236 mg. %; esters 61%; cephalin flocculation, 24 hours, trace, and 48 hours, 1+; sulfobromophthalein (Bromsulphophlein), ½ hour, 47% retention, and 1 hour, 41% retention; Takata-Ara, 24 hours, 1:64; 24-hour urine 17-ketosteroids, 12.6 mg.; protein-bound iodine, 4.2μg.

On the second hospital day an oral glucose-tolerance test was done. (Total blood sugars determined by the method of Folin and Wu.)

Time, Hr.	Sugar, Mg. %
Fasting	53
½	114
1	78
2	44
3	41
4	28

On the fifth hospital day a second glucose-tolerance test was done and serum-phosphorous determinations were done with each blood sugar. Prior to this test she had been on a 200 gm. car-



This section of the liver biopsy specimen demonstrates the irregular anaplastic cells containing hyperchromatic nuclei comprising the hepatoma. The adjacent area is essentially normal hepatic tissue; reduced 5% from mag. × 165. Reproduced with permission of the Pathology Department, Mt. Carmel Mercy Hospital.

bohydrate diet which she relished in spite of her far-advanced disease. The results of this test are as follows:

Time, Hr.	Sugar, Mg. %	Phosphorous, Mg. %
Fasting	84	3.6
½	148	3.5
1	122	3.7
2	92	2.9
3	102	4.3
5	100	4.2

On the seventh hospital day an epinephrine test was done.

Time, Min.	Sugar, Mg. %
Fasting	62
Epinephrine, 1 cc.	(1:1,000 sol.) q. s.
10	60
20	66
40	70
60	78
90	82

On the ninth hospital day a diagnostic laparotomy through a right subcostal incision was done under local anesthesia. The surgeon reported, "It was impossible to feel the edge of the liver since it was so far down into the pelvis." The liver was firmly nodular, and it was felt that the nodularity was subcapsular. A biopsy specimen was obtained, which was subsequently reported as primary carcinoma of the liver, Grade 4 (Figure). During the remainder of this hospitalization it became increasingly difficult to maintain blood sugar values above hypoglycemic levels. In spite of a good appetite, blood sugar values were in the range of 17 to 20 mg. %.

On the 14th hospital day a final oral glucose-tolerance test was done with associated phosphorous determinations.

Time, Hr.	Sugar, Mg. %	Phosphorous, Mg. %
Fasting	28	3.0
¼	80	3.5
½	68	3.4
1	57	3.2
2	40	3.4
3	25	3.7
5	42	3.5

During the remaining eight days of this hospitalization, cortisone in doses of 50 mg. every six hours was administered in an effort to influence carbohydrate metabolism, but there was no apparent beneficial effect. The patient was transferred to a convalescent home, where she died six days later. Permission for an autopsy was refused.

Comment

A discussion of the relationship of spontaneous hypoglycemia to primary carcinoma of the liver necessitates consideration of a variety of pathologic mechanisms. Admittedly, some of the evidence supporting or negating the mechanism of spontaneous hypoglycemia is speculative rather than proven. However, wherever possible, the etiologic mechanisms which follow are substantiated or discarded on the basis of data obtained from study of this case.

(*a*) *Destruction of Hepatic Tissue.*—Although the observation that extensive liver damage can produce spontaneous hypoglycemia is well documented, this clearly is not a significant factor in hypoglycemia associated with hepatoma. The type of glucose-tolerance curve associated with extensive liver damage is the "plateau curve," that is, a low fasting blood sugar, with a rapid rise following administration of glucose to hyperglycemic levels followed by a gradual decline. In contrast, the hypoglycemic curve associated with hepatoma is identical with that which occurs with organic hyperinsulinism. Here the fasting blood sugar is low, and following administration of glucose there is a rapid rise followed by an abrupt fall to hypoglycemic levels. Furthermore, it has been established by animal experimentation that more than 80% of the liver must be removed before hypoglycemia can be induced.[5] Although the liver-function studies in this case reveal a moderate degree of hepatic impairment, they do not indicate severe hepatic insufficiency. The dissociation between hepatic damage reflected in liver-function studies and occurrence of hypoglycemia was noted in the earliest reports on this disorder and was summarized by Crawford, in 1931, when he stated, "It is difficult to imagine an injury to the liver so extensive as to cause hypoglycemia and not cause other [severe †] alterations in hepatic function." [3]

(*b*) *Pressure on Unknown Intra-Abdominal Receptors.*—In recent years an increasing number of reports of hypoglycemia associated with nonpancreatic tumors has appeared in the medical literature.[5,6,8-16]

† Our insert.

These tumors, almost without exception, have been massive, and the majority have been fibromas [8-11,13,14] or fibrosarcomas. Silvis and Simon described a patient with spontaneous hypoglycemia associated with a large retroperitoneal fibroma and suggested, "It is possible that the hypoglycemia was caused by some pressure, stretching or disruptive effect on unknown receptors in the abdominal cavity." [13] This theory was based on previously reported laboratory evidence that disruption of sympathetic impulses to the liver of a cat can cause hypoglycemia.[17] It would appear unlikely that this mechanism need be seriously considered as a causal factor of hypoglycemia occurring with hepatoma or, for that matter, with any tumor. If, indeed, pressure could cause hypoglycemia, the concurrence of low blood sugars with other massive tumors and with visceromegaly, including splenomegaly and even normal pregnancies, should be but certainly is not common. Furthermore, increased intra-abdominal pressure could be conclusively excluded as an etiologic factor if spontaneous hypoglycemia occurred with a tumor situated beyond the confines of the abdominal wall. In the case reported by August, hypoglycemia resulted from an *intrathoracic* tumor.[11]

(*c*) *Secretion of a Humoral Hypoglycemia-Inducing Substance.*—The possibility that certain hepatomas and other nonpancreatic tumors could secrete insulin or a related humoral substance has been suggested by several investigators.[10-12,14] Nadler and Beers reported that the hepatomas in their two cases were "analyzed for insulin" but none was found.[1,4] However, both cases were observed more than 25 years ago, and there is no description of the method of insulin assay. There is no irrefutable evidence that nonpancreatic tumors can secrete either insulin or any other humoral substance affecting carbohydrate utilization. Skillern reported two cases of spontaneous hypoglycemia associated with large spindle-cell sarcomas and suggested that these tumors were insulin secretors because the cells resembled pancreatic β-cells and some contained blue granules.[14] This suggested tie between functional cellular activity and morphologic appearance is at most a slender thread. There seems to be little justification for the observation that "these neoplasms are actually atypical functioning islet-cell tumors," in particular since no insulin assays were done. However, August reported a case of spontaneous hypoglycemia associated with a large intrathoracic fibrosarcoma in which he stated that insulin activity in the tumor was present in an amount calculated to be three times that reported to be present in a normal pancreas.[11] That which was labeled "insulin activity" was measured by the rat-diaphragm technique of Vallance-Owen.[18] The conclusions of this study are properly qualified by the statement, "The biologic assay carried out on the tumor is a measure of insulin activity rather than the hormone itself." Whether the results of this study actually reflect tumor insulin activity or simply increased metabolic activity with excessive carbohydrate utilization is in fact a crucial issue. The common denominator of all reports of spontaneous hypoglycemia associated with extrapancreatic tumors is that these tumors are invariably massive. Little credence is lent to the supposition that nonendocrine tissue can become functionally endocrine if massive size is a necessary prerequisite.

(*d*) *Excessive Carbohydrate Utilization.*—The concept that spontaneous hypoglycemia may result from the growth of a hepatoma because the tumor avidly utilizes all available glucose, as suggested by McFadzean,[6] is supported by the following two important observations: 1. The hepatomas and other nonpancreatic tumors associated with spontaneous hypoglycemia are invariably massive in size. Since the metabolic need of a mass of tissue would of necessity increase with its size, it seems logical that a large hepatoma could conceivably divert a tremendously greater amount of available glucose for its own use than a small hepatic tumor or normal liver. The fact that hypoglycemia occurs only in association with

certain types of massive tumors, such as hepatomas, spindle-cell fibromas, and fibrosarcomas, suggests that the cells comprising these types of tumors have an unusually great affinity for glucose. 2. A fall in serum inorganic phosphorous following glucose administration has been shown by Forsham, Thorn, and others to be a valid criterion for the peripheral utilization of glucose.[19,20] If the isolated hind limb of a dog is perfused with dextrose a fall in serum inorganic phosphorous occurs. However, if the liver is similarly perfused no such fall results.[21] Therefore it can be concluded that serum inorganic phosphorous is utilized in the glycolytic cycle of skeletal muscle. Normally, glucose administered for a tolerance test, being utilized in part by skeletal muscle, causes a fall in serum inorganic phosphorous which reaches a minimum in 90 to 120 minutes. As compared to the initial level, this fall ranges between 9% and 39% and is followed by a gradual rise which approaches normal in 180 minutes.[19] In McFadzean's hypoglycemic group of hepatomas no significant drop in serum phosphorous occurred, indicating, "the dextrose administered was being diverted away from peripheral utilization, and it can only be assumed that it was being taken up by the liver." [6]

(*e*) *Absence of Glucose-6-Phosphatase.*—McFadzean demonstrated that no appreciable rise in blood sugar resulted from the subcutaneous injection of epinephrine in the hypoglycemic group of patients with hepatoma. He concluded that the remaining normal liver was depleted of glycogen and that the glycogen stores in the tumor were not metabolically available.[6] Weber and Cantero demonstrated the absence of glucose-6-phosphatase, in transplanted Novicoff rat hepatoma.[22] The role of glucose-6-phosphatase, according to Cori, is the transformation of the cellular stores of carbohydrate into blood glucose. It is possible that this enzyme is lacking in human hepatomas, thus rendering the glucose utilized by the tumor unavailable for blood glucose.

Interpretation of Laboratory Data

Evaluation of this case report supports the concept that hypoglycemia resulted from avid tumor utilization of glucose. The liver-function studies indicate moderate hepatic insufficiency but certainly not the extensive degree of damage which would be required to result in hypoglycemia. Furthermore, the glucose-tolerance curves are not the plateau type seen with extensive hepatic damage. The first glucose-tolerance test, done on the second hospital day, is a typical organic hyperinsulinism type of curve. The second glucose-tolerance test, on the fifth hospital day, is normal. This may be explained by concluding that the tumor became saturated on a high carbohydrate diet, thus allowing the residual normal liver to function. Corresponding serum inorganic phosphorous determinations reveal a significant fall (19% as compared to the initial level) in 120 minutes, indicating peripheral utilization of glucose. A third glucose-tolerance test, done on the 14th hospital day during a period in this patient's clinical course when it appeared impossible to satisfy the demands of the tumor for glucose, revealed a marked hypoglycemic curve. There was this time no associated fall in serum phosphorous but rather a gradual rise, indicating that all of the administered glucose was utilized by the tumor and none peripherally. Finally, an epinephrine test resulted in only a slight rise in blood sugar, suggesting that if glycogen stores were present in the hepatoma none was available for conversion to blood glucose. This could conceivably be explained by an absence of glucose-6-phosphatase in the hepatoma, thus interrupting the mechanism by which liver glycogen is converted to blood sugar. However, to our knowledge, no analysis for this enzyme in human hepatomas has been reported to date.

Summary and Conclusions

A case is reported of spontaneous hypoglycemia associated with a massive hepatoma.

The common denominator of all reports of nonpancreatic tumors associated with hypoglycemia is massive size.

The most logical explanation for spontaneous hypoglycemia occurring with massive nonpancreatic tumors is avid utilization of glucose by the tumors.

The possibility is suggested that the tumor glycogen is not available for conversion to blood glucose because of the absence of glucose-6-phosphatase.

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Ollier's Disease

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Dyschondroplasia, or Ollier's disease, is a developmental anomaly in which there is an abnormal growth of cartilage and in which normal ossification of cartilage fails to take place, and so, as growth continues, rounded masses or columns of cartilage remain in the metaphysis principally, and in the diaphysis occasionally, of certain bones.[1,2]

This disease, although described in most medical and radiology texts, is rarely mentioned in the American journals. It is, however, occasionally described in the European literature.

The following case is presented primarily because of its rarity and because of x-ray evidence of the prolonged and benign course of this disease.

Report of Case

The patient, a 48-year-old white man, was first admitted to the Big Spring Veterans Administration Hospital in 1953 with the complaint of pain in his left leg which had been present for one day. He stated that while a barber's chair was being loaded on a truck the chair fell and he attempted to catch it in his arms. He felt a hot searing pain in his left ankle, which worsened as the day progressed. He was seen by his private physician, who advised hospitalization for an incomplete fracture of the left tibia.

The past history revealed the patient to be a barber who worked steadily. At the age of 4 he was seen by a physician for pain in both legs, but a definite diagnosis was not made. Two years later deformity of the left arm was noted. At the age of 12 the patient was thrown from a horse and sustained a fracture of his left leg. X-rays at that time showed a bone disorder which was diagnosed as dyschondroplasia. At the age of 19 he again sustained a fracture of the left leg, which healed in about three months. He entered the Army in 1942, and in 1943 he stepped on a rock and turned his left ankle. X-ray showed a fractured left ankle for which he was hospitalized about three months. After release from the hospital he was separated from service.

The patient was born as a result of an uneventful normal pregnancy. The developmental history was apparently normal. The patient did above-average work in school. He participated in few physical activities at school, primarily because of his dislike of them. There was no known bone disease in his parents, siblings, grandparents and great-grandparents. The remainder of the past history and the review of systems were noncontributory.

Physical examination showed the patient to be a well-developed white man who was not acutely ill. The body was symmetrical except for the left upper extremity (Fig. 1). There was marked deformity of the left arm, with about 6 in. (15 cm.) of shortening. There was restricted movement of the left shoulder girdle to about 20% of normal. The elbow joint was essentially normal, but pronation and supination of the forearm was reduced about 50%. There was slight deformity of the left wrist. The left radius was about 2 in. (5 cm.) shorter than the right. In addition, there was deformity of the fingers of the left hand. The left leg showed a hard round mass about 6 cm. in diameter attached to the bone on the posterior portion of the upper end of the left tibia. There was pain and swelling of the distal third of the left tibia, with tenderness on manipulation. The remainder of the physical and the neurologic examination disclosed no other abnormalities.

Fig. 1.—Photograph of patient taken in 1957, showing shortening and deformity of left humerus.

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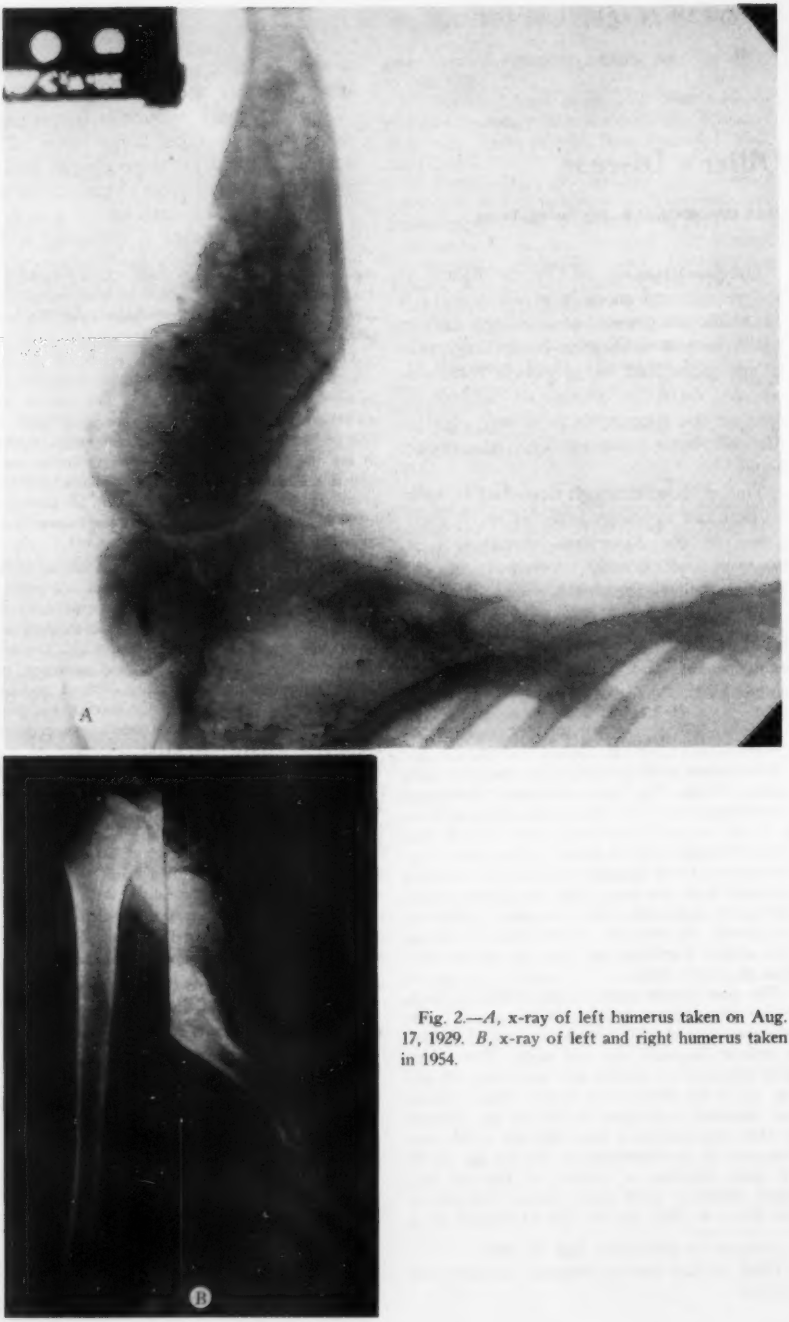

Fig. 2.—*A*, x-ray of left humerus taken on Aug. 17, 1929. *B*, x-ray of left and right humerus taken in 1954.

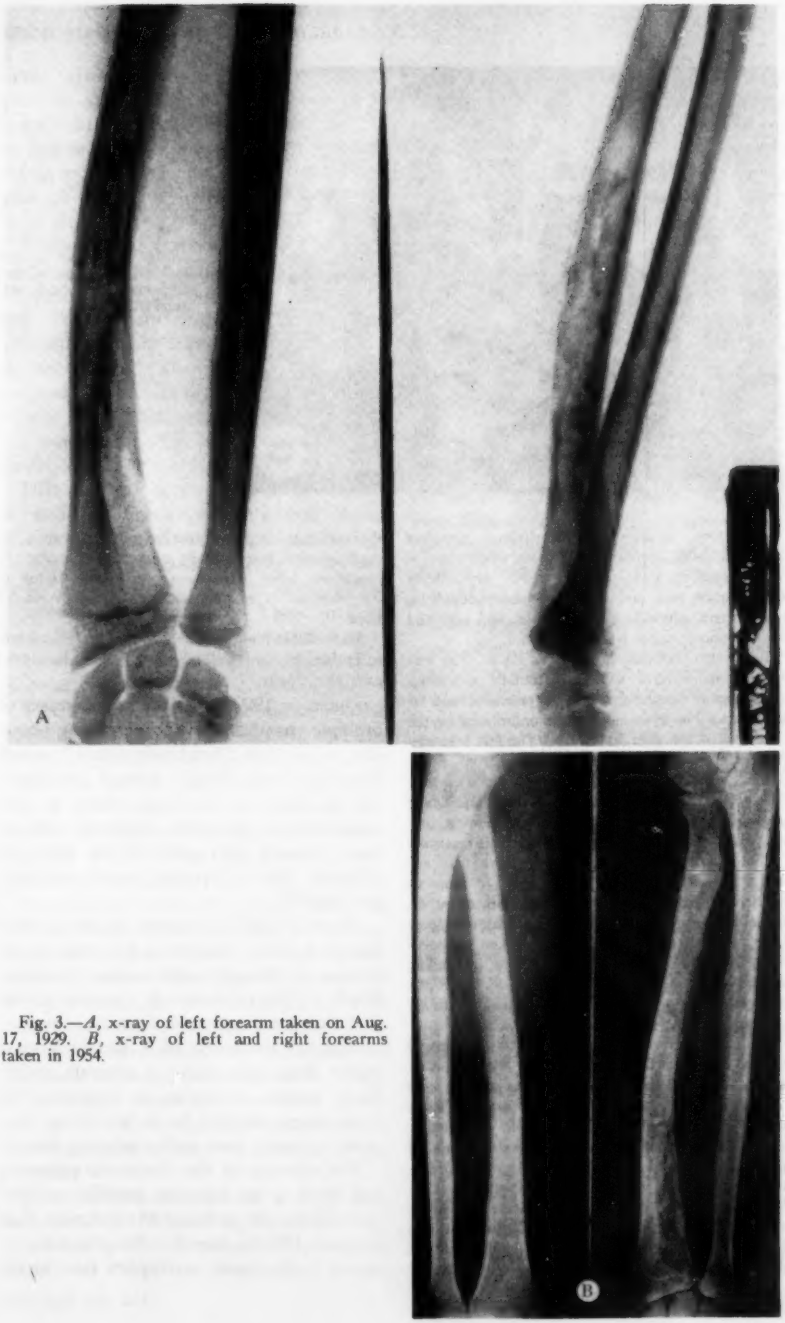

Fig. 3.—*A*, x-ray of left forearm taken on Aug. 17, 1929. *B*, x-ray of left and right forearms taken in 1954.

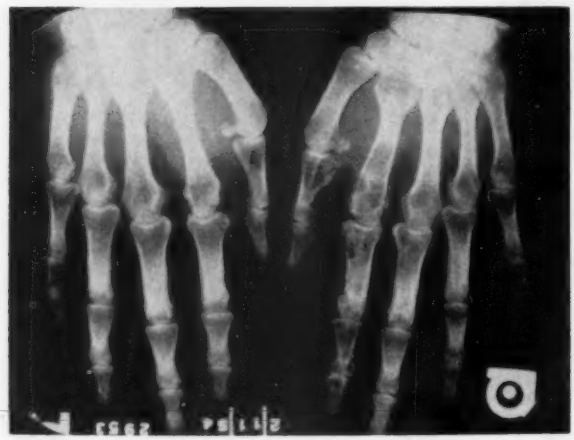

Fig. 4.—X-ray of left and right hands. (Note enchondroma only in left hand).

Laboratory examinations, including complete blood cell count, serology, urinalysis, electrocardiogram, bleeding and clotting times, erythrocyte sedimentation rate, and serum calcium, phosphorus, total protein, albumin globulin ratio, and acid and alkaline phosphatase, were all normal.

A complete skeletal survey was done. The left leg showed several osteochondromata extending laterally and medially from the proximal end of the fibula. There were also enchondromata in the distal end of the tibia and fibula. The left humerus showed marked shortening, with numerous cartilaginous rests. The right arm and leg were normal. The left foot and hand showed sclerotic and cystic areas (Fig. 4). The right foot and hand were normal. Skull plates and pelvis films were also normal.

The fracture, for which the patient was admitted, healed slowly but satisfactorily. Because of increasing pressure on the peroneal nerve on the left, a large enchondroma was removed from the upper end of the fibula, with marked improvement. Because of persistent pain in the left ankle, another enchondroma of the lower left tibia was removed, and a bone graft was placed. This healed well, and the patient recovered satisfactorily.

Pathologic examination of this tissue showed it to be one large flat piece of dense bone, measuring 8×2×5 mm. and covered on one surface with periosteum. On the undersurface was a large smooth nodular area of gray-white soft cartilaginous tissue 1×3 cm. in length and surrounded by soft cancellous bone with fatty marrow. Microscopic examination revealed benign-appearing cartilage arranged in lobular facets showing mononuclear chondrocytes. The cartilaginous stroma showed some mucoid degeneration and in places was granular with basophilic staining. Surrounding the cartilage in places and extending between the cartilaginous facets were narrow trabeculae of cancellous bone, showing some adipose tissue in the marrow. The diagnosis was enchondroma of tibia.

Since 1954 the patient has had no complaints referable to the skeletal system and has been gainfully employed as a barber.

Ollier, in 1899, described several cases of multiple chondromata affecting many bones. He called this "dyschondroplasia," which literally means "badly formed cartilage." In his cases, as in most, there is predominantly a unilateral deformity, but in some patients both sides of the body are affected. This is, however, usually not symmetrical.[2,3,5]

There is much confusion in the medical literature about the terminology and classification of chondral and osseous dysplasia. Much of this confusion is traceable to the fact that some authors believe that the dysplasias are variations of a similar disease rather than each being a separate entity. Each author attempts to improve the terminology of what he is describing, thus creating many new and confusing terms.[4]

The etiology of the disease is unknown, and there is no apparent hereditary influence. Males are probably affected more than females. Ollier's disease is found more commonly in the lower extremities than in the

upper. It is noted predominantly in the growing ends of long bones, although short bones and flat bones are also affected. It is seldom seen in the skull and vertebra. As in many developmental errors, the region of the elbow joint is singularly free from change.[2,6,8]

Grossly, the cartilage appears bluish-white, with the occasional presence of cysts. Microscopically, the cartilage shows a hyaline network very rich in cells of varying size which are usually typical and normal in appearance. There are no signs of atypical new growth or inflammation. There may be noted scattered areas of calcification and ossification. The connective tissue appears delicate.[9,10]

Diagnosis can occasionally be established at birth but is more frequently made during childhood. Clinically, the commonest sign of dyschondroplasia is dwarfing of an arm or leg, and it is for this that medical advice is most frequently sought. There may be bowing of an arm or leg, pelvic assymetry, distortion of the thoracic cage, or a marked globular expansion of the fingers or toes.[4,8]

The laboratory is of little aid in making the diagnosis. Roentgenologically, the affected long bones show abnormal shortening or bowing due to interference with longitudinal growth or more marked accumulation of cartilage on one side of the bone than the other. There is a disordered expansion of the metaphysis, with irregular, often columnar, areas of cartilage extending into the shaft. It may have a striped appearance owing to columns of bone separating the columns of cartilage. There may be a slight expansion of the cortex or even protrusion through the cortex. The epiphyseal centers are usually not disturbed, but they may be somewhat irregular in shape. It is usually stated that the clear spaces seen at the ends of the diaphysis are due to the replacement of bone by cartilage (Figs. 2 and 3).[3,7,9]

Only rarely is the shaft of a major long bone involved. When it is, it may give rise to difficulty in diagnosis. Deformities caused by large enchondromata in the phalanges are common. In older people there is a loss of demarcation of cartilaginous areas, with a tendency toward ossification and healing. X-rays of a single bone may be misleading; thus, when this disease is suspected, several bones should be x-rayed.[2,6]

The diagnosis of Ollier's disease can usually be readily made, but occasionally the osteochondromata of diaphysial aclasis can be confused with it. In diaphysial aclasis there is a hereditary history in 65% of the cases; in Ollier's disease there is no hereditary tendency. The osteochondromata of diaphysial aclasis are almost invariably pedunculated and well defined, point toward the midshaft, and may arise anywhere along the bone; in Ollier's disease the enchondromata arise near the epiphysis, are irregular, frequently contain a core of cartilage, and usually point toward the end of the bone.[2,3,7]

The prognosis as to longevity is usually good (Figs. 2*A* and 3*A*). Fractures occur readily, often with little cause, and are frequently slow to unite. Usually the condition becomes stationary after the patient reaches full growth. In some cases there are severe deformities requiring amputation. As a rule, however, there is little tendency, except in the hand and foot, for the misplaced cartilage to proliferate.[7,8]

The treatment is individualized, depending on the localization and extent of the lesion. It is believed that it is best to excise the abnormal tissues if it seems that the neighboring joint surface will be destroyed or a pathologic fracture may result or, as in our case, if the presence of the enchondroma causes pain or disability.[7]

Summary

A case of Ollier's disease with x-ray evidence of the disease for over 25 years, is described. A review of the salient features of the disease is also presented.

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Pulmonary Changes Associated with Hexamethonium Therapy

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Since 1953 several reports of pulmonary lesions developing concurrently with hexamethonium therapy for hypertension have been recorded. The lesions have been described as similar but not always identical to acute diffuse interstitial pulmonary fibrosis as described by Hamman and Rich.[1]

In 1953, Morrison [2] reported 39 cases of hypertension treated with parenteral hexamethonium, with the development of dyspnea and bilateral symmetrical opacities on chest roentgenograms in three patients treated for 7, 9, and 15 months, respectively. One of these patients died, and autopsy revealed extensive central carnification of both lungs. A subsequent report by Doniach, Morrison, and Steiner,[3] apparently on the same three patients, showed both an intra-alveolar and an interstitial pulmonary fibrosis in the two patients who died. One patient recovered, with improvement as observed in the chest x-ray.

Morrow, Schroeder, and Perry [4] mention five cases of hypertension treated with hexamethonium and hydralazine in which interstitial pneumonitis developed, considered to be identical pathologically to the type of fibrosis described by Hamman and Rich.[1] All of their patients died within a week after developing pulmonary symptoms without cor pulmonale, as seen in the Hamman-Rich syndrome.

Robillard and associates [5] also report a 28-year-old woman treated with hexamethonium for nine months who developed lung changes featured by early fibrosis of the alveolar walls and a mononuclear-cell interstitial infiltrate, with some serous fluid in the alveoli, containing a few leukocytes and erythrocytes. No intra-alveolar fibrosis developed in this case.

The following fatal case was considered to be that of malignant essential hypertension with terminal bronchopneumonia, both from a clinical standpoint and at the initial postmortem examination. However, microscopic review reveals what we believe is another example of the interstitial pneumonitis which may be seen in association with hexamethonium therapy.

Report of Case

A 55-year-old automobile dealer was admitted to St. Luke's Hospital on Jan. 7, 1953. One month prior to admission the patient noted sudden right homonymous hemianopsia, which subsequently gradually improved. For six days preceding admission he had complained of cough, chills, fever, and generalized weakness.

Past history revealed that the patient had been admitted four times previously, beginning in 1951, for evaluation and treatment of essential hypertension. During the first admission, in April, 1951, the blood pressure was 230/130 mm. Hg and the fundi showed marked focal arteriolar spasms and hemorrhages. He was treated with veratrum viride, potassium thiocyanate, and phenobarbital, with little benefit. During hospitalization in March, 1952, therapy included a salt-free diet, natranil, alkavervir (Veriloid), and potassium triplex. The N. P. N. was 43 mg. % at this time. In May, 1952, while hospitalized, the patient received oral and parenteral hexamethonium, the systolic blood pressure ranging from 170-210 mm. Hg and the diastolic from 95-120 mm. Hg. He continued to receive 3 gm. of hexamethonium per day orally at home. The fourth admission was in October, 1952. The N. P. N. was 57 mg. % at this time. He was dismissed to receive 1.5 gm. of hexamethonium orally daily. On the fifth, and final, admission physical examination revealed a blood pressure of 255/145 mm. Hg; pulse, 88, and temperature, 98.2 F, orally. A right homonymous hemianopsia

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was present. Moderately severe retinal arteriolar narrowing was seen. The lungs were normal to vocal fremitus and percussion, but the breath sounds were slightly decreased over the right posterior lung base. The remainder of the physical examination was not remarkable. Laboratory findings were hemoglobin, 12 gm. %; red blood cell count, 3,310,000, and white blood cell count, 7,150. Urinalysis revealed specific gravity, 1.008, a trace of albumin, granular casts, occasional white blood cells, and 1-2 red blood cells per high-power field. The N. P. N. was 72 mg. %; potassium, 5.5 mEq. per liter; carbon dioxide, 23 mEq. per liter; sodium, 151 mEq. per liter, and chloride, 107 mEq. per liter.

The initial admission diagnosis was essential hypertension, small left occipital lobe hemorrhage or thrombosis, and upper respiratory tract infection. During the four days following admission fever (temperature of 101 F to 102 F) occurred in the early evening, the temperature receding to near-normal levels by morning. A total of 3.4 ml. of Veratrone (a purified preparation of veratrum viride), containing 0.85 mg. of veratrum alkaloids, was given during this period in an attempt to lower the blood pressure. However, systolic levels of 185-230 and diastolic levels of 100-130 mm. Hg persisted. Five days after admission the lungs were clear, although respiration was rapid and shallow. The patient was placed in an oxygen tent, and a blood culture was done, which was negative. A repeat blood cell count showed 11.2 gm. of hemoglobin, 3,500,000 red blood cells, and 15,000 white blood cells, with 86% neutrophils. Six days after admission, the day preceding death, the axillary temperature varied from 99 F to 103 F and the blood pressure continued at levels of 220-250 systolic and 120-130 diastolic. The patient was irrational and cyanotic, with rapid shallow respirations. Inspiration was decreased in the left chest; many moist rales were heard at both lung bases, and a gallop rhythm with a rate of 120 was heard. No dullness or increased vocal fremitus was noted. The sedimentation rate (Westergren) was 16.5 mm. in one hour, and the N. P. N., 105 mg. %. Bronchopneumonia was considered to be present, and 100,000 units of aqueous penicillin was given intramuscularly every three hours. The patient was given 100 mg. of hexamethonium subcutaneously during the early morning of Jan. 14, but the blood pressure persisted at levels of 230-250 systolic and 130-150 diastolic. The patient died suddenly on Jan. 14, 1953, seven days after admission.

At autopsy the right pleural cavity contained 300 cc. and the left pleural cavity 200 cc. of clear yellow fluid. The heart weighed 550 gm. Moderate coronary and aortic atherosclerosis were present, with ulcerated plaques in the abdominal aorta. The right lung weighed 1,000 gm. and the left lung 850 gm. On cut section both lower lobes were firm, with an appearance somewhat suggestive of red hepatization. The upper lobes and right middle lobe showed a moderate loss of elasticity and on cut section were slightly congested, with scattered raised red areas. The right kidney weighed 110 gm. and the left kidney 120 gm. The capsules stripped with slight difficulty, revealing coarsely granular surfaces. The corticomedullary junction of each kidney was poorly defined. The brain contained a 3.5 cm. area of softening and hemorrhage in the left occipital lobe.

The significant microscopic findings were confined to the heart, brain, kidneys, and lungs. The heart showed hypertrophy of the muscular fibers. The occipital lobe of the brain contained an area of encephalomalacia and old hemorrhage. The kidneys were the seat of an advanced arteriolar sclerosis, and the medium-sized arteries also showed varying degrees of thickening. Scarring, leukocytic infiltration, and variable degrees of mild to severe tubular and glomerular degenerative changes were very prominent features. An incidental finding was a small benign papillary adenoma in one kidney. The lungs showed passive hyperemia, patchy edema, emphysema, and focal atelectasis in many areas, but the most striking alteration was the presence of an organizing exudate in many of the alveoli and atria where the lumina were filled with masses of fibroblasts and the alveolar walls were often thickened and fibrosed (Figs. 1 and 2). In these areas of carnification, the alveolar outlines could usually be identified, and sometimes the lining cells were greatly swollen. In other foci the alveoli contained masses of fibrin, and in others the fibrin was penetrated by a few fibroblasts. These variable stages suggest different ages of the exudate. Elastica stains in the organized areas revealed a normal alveolar elastic-tissue distribution.

Comment

The pathological changes in the case reported herein appear to resemble previously recorded pulmonary changes associated with hexamethonium therapy. Unfortunately no chest films were taken during the final hospital admission, since the clinical findings appeared typical of bronchopneumonia. This case showed an advanced degree of intra-alveolar fibrosis compatible with the relatively long period of hexamethonium administration (eight months). Carnification of the lung ordinarily is due to organization of the exudate

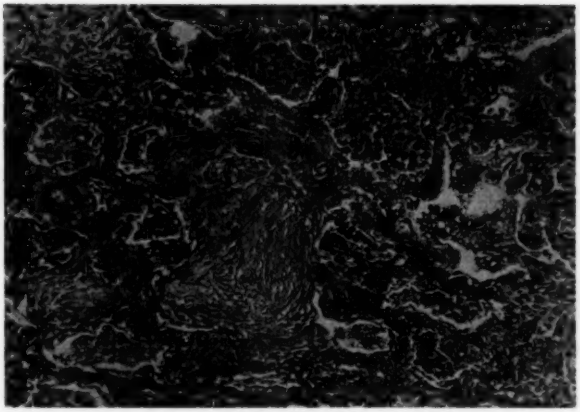

Fig. 1. — Photomicrograph of lung, showing an organizing exudate of fibrocytes filling alveoli and atria, with some of these spaces being relined with cuboidal cells; reduced 40% from mag. × 165.

of an unresolved lobar pneumonia. However, in this case there is no evidence for such a hypothetical pathogenesis. A likely possibility would seem to be that a marked effluence of fibrin-rich fluid into the alveoli and atria occurred, possibly the result of minor attacks of lung edema, with lack of absorption of the exudate and subsequent fibroblastic replacement. Moreover, the varying stages of pure fibrin, partially organized fibrin, and pure fibroblastic masses in the alveoli would point to possibly several episodes of exudation. Doniach, Morrison, and Steiner [3] have suggested that such attacks may be at least partially alleviated by hexamethonium treatment and the patient thus permitted to survive long enough to organize the fibrin-rich exudate.

There are speculative aspects to this case which give one pause for thought regarding the broad philosophy of collagen diseases. For example, it is known that penicillin and hydralazine are associated with a rheumatoid syndrome complete with L. E. cells and systemic disease. These could be considered drug reactions. It is also known that the

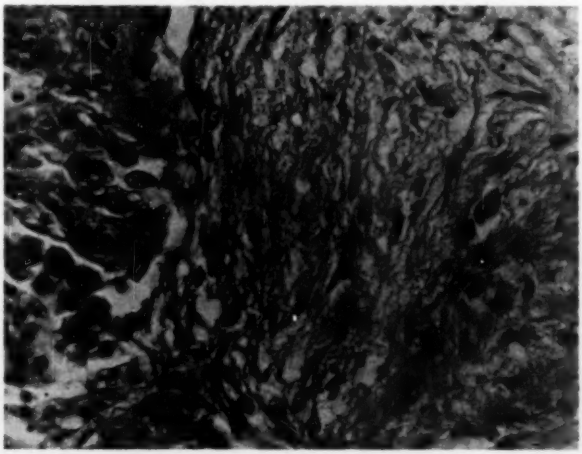

Fig. 2. — Photomicrograph of lung, showing in higher power the character of the fibrocytic organization of the older exudate; reduced 30% from mag. × 500.

antimalarial drugs, quinacrine (Atabrine) and chloroquine, will suppress the clinical manifestations of many cases of disseminated lupus erythematosus, although they do not abolish the L. E.-cell phenomenon. Cortisone has clinically if not physiologically similar effects. Here then is another drug, hexamethonium, which seems to bring on a collagen-type disease which, in the cases reported, is largely confined to pulmonary tissue.[6] It becomes increasingly important, therefore, to discover if other ganglionic blocking agents, such as pentolinium (Ansolysen) or mecamylamine (Inversine), might have similar effects. It is also important to note, as has been repeatedly pointed out in the past, that the modern drugs at our command are not innocuous, and perhaps our ideas on their toxic side-effects are falsely secure because we do not often report therapeutic casualties. At any rate, we now have chemical means of producing what appears to be a collagen-disease syndrome on the one hand, and we have a chemical means, namely cortisone, of relieving the symptoms of this syndrome on the other hand.[7] Cortisone and corticotropin (ACTH) are reported to benefit interstitial pneumonitis in some cases, although withdrawal may precipitate death. It would seem perhaps only necessary for the biochemist to decipher the cellular physiology involved in order that we may be enlightened as to the actual pathogenesis of these diseases.

Summary

A case of malignant hypertension treated with hexamethonium for eight months is reported which at autopsy showed the previously described changes associated with hexamethonium therapy. The relationship of this case to the Hamman-Rich syndrome is discussed.

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Treatment in Internal Medicine

Combined Antibiotic Therapy in Serious Infections Caused by Drug-Resistant Staphylococci (1956-1957)

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The occurrence of severe systemic infections caused by drug-resistant staphylococci currently forms a serious threat to the effective medical and surgical management of hospitalized patients. These drug-resistant organisms occur in high density in hospitals all over the world, and treatment of the infections caused by them presents an outstanding challenge to antimicrobial therapy. Such serious infections tend to occur in patients whose normal host defenses against infection are impaired.[1,2] The unusual versatility of staphylococci permits the rapid emergence of variants resistant to any newly developed drug which is used on a large scale in the hospital environment. Therapy with single drugs often fails in serious staphylococcal infections because transient suppression of the drug-susceptible infecting organisms is rapidly followed by the emergence of a predominantly drug-resistant microbial population. Therefore combined antimicrobial therapy has been widely practiced for the management of such serious staphylococcal infections. In spite of apparently vigorous therapy, the over-all mortality from serious staphylococcal infections in many hospitals is probably 50% or greater and resembles that of the preantibiotic era.

One factor which undoubtedly contributes to these unsatisfactory therapeutic results is the generally debilitated state of the patients who are most likely to develop staphylococcal sepsis. Another is the possibility that drugs for treatment are not selected to best advantage. It is conceivable, for example, that bactericidal drug combinations might be necessary for cure not only in endocarditis[2-4] but also in septic states where the impaired host defenses are inadequate to eliminate infecting organisms merely suppressed by chemotherapy.[2] Yet other factors might be the failure to employ well-timed surgical drainage of pus collections or to achieve adequate drug levels in areas not readily reached by drugs in the systemic circulation.

For some years we have been interested in the mechanisms of combined-antibiotic action and have formulated concepts applicable to the rational selection of drug combinations in clinical practice.[5] A laboratory test which aids in the selection of drug pairs bactericidal for a given micro-organism was proposed some time ago.[6] After more than five years of experience with this test we believe that, properly interpreted in the light of clinical judgment, it may provide valuable guidance to the selection of antibiotic combinations for the treatment of drug-resistant infections. It is the purpose of this paper to present cases which illustrate our use of this method and to propose an approach to the management of drug-resistant staphylococcal infections which appears to have been successful in our hands.

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Materials and Methods

Patients.—All patients studied were referred to me for consultation during 1956 and 1957. The reason

for referral was most commonly the lack of response to initial chemotherapy in an apparently serious staphylococcal infection. Thus this is a highly select group of patients, not comparable to the usual hospital series. The time limits (20 months in 1956 and 1957) are important with reference to the particular drugs employed; such drugs might not have been available earlier or might be ineffective at a later date. All patients discussed here were followed for a minimum of four months after the end of antimicrobial therapy to give meaning to the claim of bacteriological cure.

Laboratory Evaluation of Combined Antibiotic Action.—The etiologic Staphylococcus pyogenes var. aureus, hemolytic and coagulase-positive, was available in each case. In 8 of the 11 patients presented in detail it was grown from blood cultures; in the others, from sputum, pleural fluid, or joint fluid. In most instances disk type sensitivity tests were performed on the organism in addition to the test described below. All staphylococcal strains described here grew freely in 10 units per milliliter of penicillin. In 9 of the 11 patients it was virtually certain that the infection had been acquired in a hospital, and in the two others there was known contact with hospital environment.

The method employed for the evaluation of combined-antibiotic action against a given strain of Staphylococcus was an adaptation of the procedure published earlier.[8] The aim of the method is to determine (*a*) the ability of clinically useful single antibiotics to inhibit or rapidly kill a large inoculum of bacteria in a concentration which can be achieved readily in tissue or body fluids by maximal well-tolerated doses of each drug, (*b*) the ability of certain drug pairs to achieve the same end, and (*c*) the possible advantage of a drug pair over its constituent members in producing a rapid bactericidal effect or protracted inhibition through the delay of emergence of resistant variants.

The following technique was employed:

To tubes containing proteose peptone No. 3 broth (Difco) antibiotics were added to give the following concentrations in a volume of 10 ml.±0.5 ml. (amounts per milliliter):

Penicillin 10 units
Bactitracin 1 unit
Streptomycin 20μg.
Chloramphenicol 20μg.
Tetracycline 10μg.
Erythromycin 2μg.
Neomycin 2μg.
Novobiocin 4μg.
Vancomycin 4μg.
Ristocetin 10μg.

Penicillin 10 units	+ streptomycin 20μg.
	+ bacitracin 1 unit
	+ chloramphenicol 20μg.
	+ tetracycline 10μg.
	+ erythromycin 2μg.
Bacitracin 1 unit	+ streptomycin 20μg.
	+ tetracycline 10 μg.
	+ chloramphenicol 20μg.
	+ novobiocin 4μg.
	+ erythromycin 2μg.
Streptomycin 20μg.	+ tetracycline 10μg.
	+ chloramphenicol 20μg.
	+ erythromycin 2μg.
Neomycin 2μg.	+ tetracycline 10μg.
	+ chloramphenicol 20μg.
	+ erythromycin 20μg.
	+ novobiocin 4μg.
Novobiocin 4μg.	+ chloramphenicol 20μg.
	+ erythromycin 2μg.

Each tube was inoculated with 0.1 ml. of a 1:10 dilution of an 8- to 14-hour broth culture of the Staphylococcus, resulting in a bacterial concentration of 10^4-10^5 organisms per milliliter of broth containing antibiotic at the beginning of incubation. After 20-22 hours of incubation at 37 C the turbidity (denoting growth of the inoculum to a level of more than 10^7 organisms per milliliter) was recorded for each tube. From tubes remaining clear (i. e., showing either inhibition or killing of bacteria) one loopful (0.02 ml.) was subcultured onto one-sixth of a blood agar plate. Tubes and plates were incubated for another 24 hours. At the final reading the turbidity at the end of 48 hours' incubation was recorded and the number of colonies in each subculture estimated. For each tube (containing either a single drug or a drug pair) the following reading was recorded:

(*a*) Visible turbidity present in 24 hours: no significant inhibition.

(*b*) No turbidity present in 24 hours but some turbidity in 48 hours: temporary inhibition.

(*c*) No turbidity in 24 and/or 48 hours, on subculture more than 100 colonies: complete inhibition but negligible bactericidal effect.

(*d*) No turbidity in 24 hours, on subculture less than 5-20 colonies: significant bactericidal effect.

Principles in Selection of Drugs for Treatment.—Drugs for initial treatment were selected on the basis of recent experience with staphylococcal disease in this community and consideration of the specific treatment problem in each case. The drug regimen was modified in the light of the results of laboratory tests for inhibitory and bactericidal activity of single or paired drugs. The dose, route, and duration of drug administration were designed to eradicate the infection organism at its principal sites of multiplication. Whenever drugs with marked potential toxicity were employed (e. g., bacitracin, neomycin, novobiocin) renal function

and blood counts were evaluated frequently. In the use of these drugs the risk of toxicity was constantly weighed against the risk of death from the infection if the particular agent were not employed.

Report of Cases

Staphylococcal Deep-Wound Infection

CASE 1.—A 54-year-old man entered the hospital on Nov. 22, 1957, for an endarterectomy to relieve obstruction of superficial femoral arteries caused by arteriosclerosis obliterans.

The patient was known to have had hypertension and arteriosclerosis obliterans at least since 1956. In December, 1956, he underwent a left lumbar sympathectomy and bilateral renal endarterectomy. Subsequently he suffered from marked claudication of the lower extremities. Aortograms confirmed the presence of occlusion of the superficial femoral arteries.

On admission his blood pressure was 190 systolic and 90 diastolic. There was moderate arteriovenous nicking in the fundi. Both femoral pulses were present, but the popliteal, tibial, and dorsalis pedis pulses were absent. Apart from the vascular disturbances the physical examination was unremarkable.

Laboratory examination showed a PCV of 44 and a white blood cell count of 8,200, with 54% polymorphonuclear leukocytes and 45% lymphocytes. Findings on examination of the urine were within normal limits. Creatinine clearance was diminished to 43 ml. per minute.

On Nov. 23 an endarterectomy of the right superficial femoral artery was performed without difficulty. The early postoperative course was uneventful, and peripheral circulation in the right leg was markedly improved. On the 15th postoperative day, Dec. 8, the temperature rose abruptly to 103.6 F. (39.8 C) and redness and induration appeared along the right common femoral artery near the operative site. The white blood cell count was 17,200, with 86% polymorphonuclear leukocytes. A blood culture grew out S. pyogenes var. aureus, hemolytic. Swinging fever continued, and on Dec. 10 there was definite bulging along the femoral incision, with redness, warmth, and tenderness. The area was incised and an old hematoma and pus drained. Cultures from the area yielded S. pyogenes var. aureus. At the time of drainage the patient was given antimicrobial therapy, consisting of chloramphenicol, 2 gm.; novobiocin, 2 gm., and erythromycin, 2 gm., daily by mouth. There was prompt defervescence, and the patient's appearance improved. During examination of the draining wound, on Dec. 11, there was a sudden rupture of the femoral artery. Bleeding was temporarily stopped by pressure. Immediate operation revealed infection of the old arterotomy suture line and rupture of a small aneurysm of the right common femoral artery. The common, superficial, and profunda femoral arteries were ligated to control hemorrhage.

Subsequently infection subsided rapidly, and on Dec. 20 all antimicrobial drugs were discontinued. However, the right leg had to be amputated subsequently because of insufficient blood supply.

Comment: This patient presents the simplest form of staphylococcal deep-wound infection. Bacteremia in such cases is the result of seeding the blood stream from the site of suppuration. Adequate drainage of that site often suffices for control of the infection, even without antimicrobial therapy. Suppressive antistaphylococcal drugs, like erythromycin, chloramphenicol, or novobiocin, speed recovery. While these drugs may be used in combination to avoid the rapid emergence of resistant variants, a bactericidal drug effect is *not* necessary for cure. Therefore we have *not* applied the test for combined-antibiotic sensitivity in such cases, unless the response to drainage, debridement, and simple antimicrobial therapy was unsatisfactory.

Five similar clinical cases have indicated to us that, while this type of infection is readily controlled, it nevertheless may be disastrous to the patient, because it may destroy the results of an elective and potentially remedial surgical procedure.

Staphylococcal Endocarditis

CASE 2.*—A 34-year-old Chinese man entered the hospital on Oct. 19, 1957, because of chills and fever for two weeks.

For some years the patient was known to have had a heart murmur. He also had suffered from widespread eczema, severest on his legs. In September, 1957, he was hospitalized for two weeks for treatment of the skin disorder, receiving both topical and systemic antimicrobial drugs at that time, as well as topical corticosteroids.

Some days after his return home, in September, he developed a respiratory illness which lasted for four days. He recovered from it, but a few days later, in early October, he relapsed and developed chills, fever (temperature to 102.2 F. [39 C]), weakness, and malaise. He was treated at another hospital with several antimicrobial agents, chosen on the basis of "disk" tests, without response. His fever increased; he developed marked air hunger,

* Reported with permission of Dr. S. P. Lucia.

and he was therefore transferred to the university hospital.

On admission the patient appeared apprehensive, dyspneic, and acutely ill. His temperature was 101.8 F (38.8 C); his blood pressure, 140 systolic and 80 diastolic. He had severe chronic atopic dermatitis on both lower legs. There were petechiae on the eyelids and several exquisitely tender red nodules on the toes. The heart was somewhat enlarged, and a blowing systolic murmur was heard over the entire precordium. Both liver and spleen were slightly enlarged and tender.

Laboratory examination on admission showed a hemoglobin concentration of 10.3 gm. per 100 ml. of blood and a white blood cell count of 13,850, with 74 polymorphonuclear leukocytes, 17 lymphocytes, and 7 monocytes. The urine contained a trace of protein, and there were 3-5 red and 10-15 white blood cells and occasional hyaline casts in the sediment. Blood cultures revealed large numbers of hemolytic coagulase-positive S. pyogenes var. aureus. Antibiotic sensitivity determinations of this organisms gave the following results:

It was markedly inhibited by tetracycline, 10μg. per milliliter, or erythromycin, 2μg., and slightly and transiently inhibited by penicillin, 10 units per milliliter; bacitracin, 1 unit; chloramphenicol, 20μg.; novobiocin, 4μg., or neomycin, 2μg.

The following drug combinations were both completely inhibitory and rapidly bactericidal (amounts per milliliter):

Penicillin 10 units + tetracycline 10μg.
Bacitracin 1 unit + tetracycline 10μg.
Novobiocin 4μg. + chloramphenicol 20μg.
Neomycin 2μg. + tetracycline 10μg.
Neomycin 2μg. + erythromycin 2μg.

Several other antibiotic combinations had less marked effects.

On Oct. 21 the infective organism was isolated from the first blood culture, and on the basis of finding a hemolytic Staphylococcus as the cause of endocarditis treatment was begun empirically with penicillin, 20,000,000 units; bacitracin, 80,000 units; chloramphenicol, 2 gm., and novobiocin, 2 gm., daily. When the antibiotic-sensitivity determinations became available, tetracycline, 2 gm. daily, was added to the regimen. There was rapid defervescence, and all blood cultures obtained after Oct. 25 remained negative. The course of treatment was uneventful except for the sudden development of high fever on Nov. 12, when the site of an intramuscular catheter for the administration of penicillin became acutely inflamed. From the drainage Candida albicans was cultured. The catheter was removed and penicillin administration discontinued. The local inflammation subsided promptly with application of heat. During treatment some proteinuria and hematuria continued but there was no significant rise in the nonprotein nitrogen or creatinine levels in the blood. All antibiotics were discontinued on Nov. 25, and a few days later the patient was discharged home. Prolonged follow-up has confirmed cure of the infection.

Case 3.†—A 64-year-old white priest entered the hospital on March 6, 1957, because of chills and fever.

He had been fairly well in the past except for a duodenal ulcer some 10 years earlier, which recurred in 1955 and promptly responded to treatment, and an attack of ankle edema in 1954, which responded to a high-protein and high-vitamin diet.

About March 1, 1957, he noted very marked general malaise. On March 4 there was severe muscle aching and headache, some difficulty in breathing, and a nonproductive cough. These symptoms persisted upon bed rest, and on March 6 there was fever, with temperature up to 102.9 F (39.4 C).

On admission the patient appeared acutely ill and prostrated, coughing frequently. The temperature was 102.6 F (39.2 C). Rales were heard at both lung bases. The heart was not enlarged; the rhythm was regular, and the sounds were of normal quality. A rough Grade 3 systolic murmur was heard over much of the precordium. There was no diastolic murmur and no friction rub. The remainder of the physical examination was not contributory.

Repeated blood cultures were obtained on the day of admission. All yielded large numbers of hemolytic S. pyogenes var. aureus. By disk test, the organism was most sensitive to tetracycline and also was inhibited by erythromycin, novobiocin, oleandomycin, or streptomycin.

The patient was treated with a succession of these drugs between March 6 and May 17 (as shown in Chart 1), but there was either no clinical response and persistent positive blood cultures or only a temporary response followed by clinical and bacteriological relapse.

During his relapse in May, 1957, the S. pyogenes var. aureus cultured from the blood stream was subjected to antibiotic-sensitivity determinations measuring bactericidal effects of single drugs and combinations. The organism still was inhibited by bacitracin, 0.2 unit per milliliter; streptomycin, 20μg.; chloramphenicol, 25μg.; tetracycline, 2μg.; erythromycin, 2μg., or novobiocin, 4μg., but none of these was rapidly bactericidal. The following drug combinations (and a number of other combinations) appeared to be both completely inhibitory and rapidly bactericidal in vitro (amounts per milliliter).

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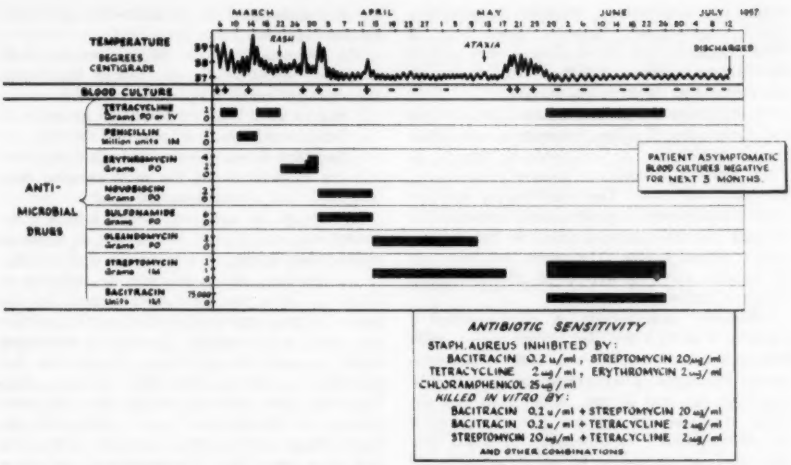

Chart 1.—Clinical course of Case 3. Bacterial endocarditis due to S. pyogenes var. aureus.

Bacitracin 0.2 unit + streptomycin 20μg.
Bacitracin 0.2 unit + tetracycline 2μg.
Streptomycin 20μg. + tetracycline 2μg.
Bacitracin 0.2 unit + chloramphenicol 25μg.
Bacitracin 0.2 unit + erythromycin 2μg.
Streptomycin 20μg. + erythromycin 2μg.
Bacitracin 0.2μg. + novobiocin 4μg.

Combined treatment with tetracycline, 2 gm.; bacitracin, 100.0 units, and streptomycin, 2 gm. (Chart 1), daily, was instituted, because these drugs were exceedingly rapidly bactericidal in vitro and could be conveniently administered. This treatment continued from May 29 through June 26, 1957. A slight disturbance of equilibrium developed during therapy but disappeared in subsequent months. All blood cultures taken after the beginning of therapy were negative. The patient was discharged from the hospital, apparently well, on July 13, 1957. Follow-up examinations through December, 1957, indicate that he is entirely well and working.

Comment: These two cases illustrate once more that for the cure of bacterial endocarditis it is essential to employ rapidly bactericidal drugs. The "disk" test, which measures only inhibitory activity, is largely useless and may be misleading.[3,7] The simultaneous use of more than two drugs might be criticized. In theory, any rapidly bactericidal drug pair might have sufficed for cure. However, our experience with staphylococcal endocarditis until 1956 had been discouraging in that over one-half of the patients died from either organic cardiac damage, massive cerebral embolism, or apparently uncontrolled infection. This led us to employ simultaneously several drug pairs which appeared rapidly bactericidal in vitro and not to treat any staphylococcal endocarditis with less than three drugs. The success in the present cases may be associated with this approach.

Case 4.‡—A 37-year-old white married nurse entered the University Hospital on Oct. 7, 1957, because of recurrent chills and fever since mid-August, 1957.

About Aug. 10 the patient had induced an abortion in the fifth month of pregnancy by means of inserting a catheter into the uterus. Shortly thereafter she developed chills and fever. Because of persistent bleeding, dilatation and curettage was performed, on Aug. 13, to remove retained placenta. The procedure was followed by chest pain and "pleurisy."

Blood cultures were repeatedly positive for hemolytic S. pyogenes var. aureus in spite of treatment with penicillin and streptomycin. Administration of erythromycin, beginning Aug. 23, made the patient temporarily afebrile, but about 10 days later the fever returned and blood cultures were positive again. The addition of chloramphenicol, on Sept. 12, had no effect, and these two drugs were discontinued on Sept. 16. From that date on, novo-

‡ Reported with permission of Dr. H. D. Brainerd.

biocin was administered, resulting in temporary clinical improvement. However, about Sept. 27 fever reappeared and blood cultures were positive for the same organism. For that reason the patient was referred to the university hospital.

On admission the patient appeared both acutely and chronically ill. The temperature was 102.2-104.0 F (39-40 C); B. P., 110/65; P, 100; R., 28. There were no petechiae or splinter hemorrhages. The lungs were clear. The heart was not enlarged, and the sounds were of good quality. Intermittently a Grade 2 systolic murmur could be heard along the left sternal border. The spleen and liver were not palpable, and there were no abdominal or pelvic masses or tenderness.

Laboratory examinations on entry showed a hemoglobin of 12.5 gm. per 100 ml. and a white blood cell count of 4,300, with 56% polymorphonuclear leukocytes. The corrected erythrocyte sedimentation rate was 36 mm. in one hour, and the serum creatinine, 0.8 mg. per 100 ml. Chemical and electrophoretic measurements of blood proteins were within normal limits. Examination of the urine gave entirely normal results.

Repeated blood cultures yielded hemolytic S. pyogenes var. aureus (50 to 500 colonies per milliliter of blood). The organism was not significantly inhibited by penicillin, 50 units per milliliter; streptomycin, 20μg.; tetracycline, 10μg.; neomycin, 2μg. It was markedly inhibited by bacitracin, 1 unit per milliliter; chloramphenicol, 20μg.; erythromycin, 2μg.; vancomycin, 10μg.; ristocetin, 5μg., or novobiocin, 4μg. Bacitracin and erythromycin also appeared to be somewhat bactericidal for the organism.

The following antibiotic combinations were both completely bacteriostatic and rapidly bactericidal (amounts per milliliter):

Bacitracin 1 unit + penicillin 10 units
Erythromycin 2μg. + penicillin 10 units
Bacitracin 1 unit + chloramphenicol 20μg.

X-ray examination of the chest revealed clear lung fields and a normal cardiac shadow.

In view of the extremely severe infection, the patient was started soon after entry on combined antimicrobial therapy with bacitracin, erythromycin, chloramphenicol, and novobiocin, as indicated in Chart 2. There was some defervescence, but the blood cultures remained positive until penicillin was added to the regimen. During the subsequent month on antimicrobial therapy it appeared that the infection might be controlled. However, when the drugs were discontinued, on Nov. 25, there was an immediate clinical and bacteriological relapse. Blood cultures remained positive even after antibiotics (penicillin, chloramphenicol, and novobiocin) had been started again, evidently because the combined effect of penicillin and bacitracin was required for suppression of the staphylococci. An exploratory laparotomy was performed on Dec. 18 because of the possibility that an abscess in the abdomen or pelvis might be seeding the blood stream. No suggestive lesion was found anywhere in the course of surgical inspection. Because the Staphylococcus cultured from the blood stream on many occasions was strongly inhibited by risto-

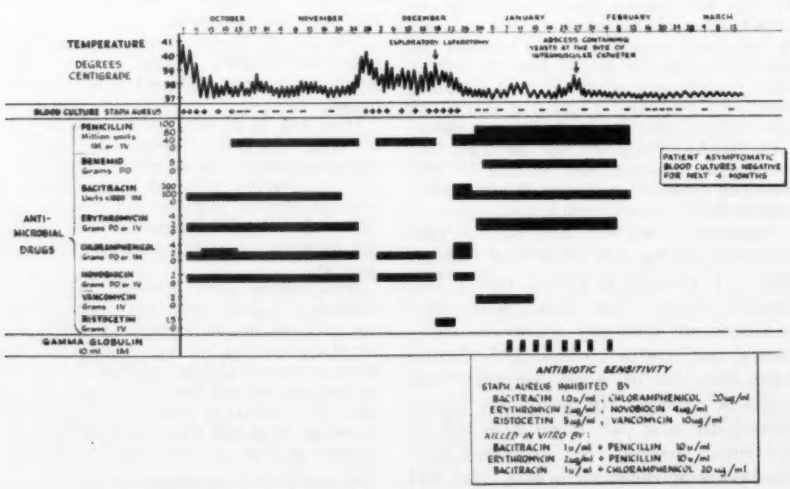

Chart 2.—Clinical course of Case 4. Staphylococcus sepsis following induced abortion.

cetin, 5μg. per milliliter, this drug alone was experimentally administered from Dec. 18 through 22 in a dose of 1,500 mg. daily, given as intravenous drip in a 5% dextrose solution. All blood cultures taken on these days were positive, although blood serum had a marked inhibitory activity for the organism in vitro. The inhibitory activity extended through a serum dilution of 1:32 and was most pronounced in a serum dilution of 1:8 and less marked with undiluted serum.

As ristocetin exerted neither a clinical nor a bacteriological effect it was discontinued, and the patient was again placed on combined therapy with penicillin, bacitracin, chloramphenicol, and novobiocin. Prompt suppression of symptoms and negative blood cultures resulted. However, it was doubtful that this drug regimen would accomplish cure, as it had failed before. Consequently the patient was switched to combined therapy consisting of penicillin, 100,000,000 units; probenecid (Benemid), 3 gm.; bacitracin, 100,000 units; erythromycin, 3 gm., and vancomycin, 2 gm., daily (Chart 2). Since the beginning of this regimen all her blood cultures remained negative. Vancomycin administration was discontinued after 14 days, the other drugs, after 6 weeks. The patient improved steadily and showed no signs of active infection except for the development of an abscess due to yeasts at the site of an intramuscular catheter. This subsided spontaneously. After the cessation of antimicrobial therapy the patient continued to gain weight and strength. All blood cultures taken during the subsequent four months have remained sterile.

Comment: While it is not fully established that this patient actually suffered from bacterial endocarditis, it appears to be the most probable diagnosis to explain the behavior of her protracted sepsis. This case illustrates clearly that the in vitro selection of antimicrobial drugs is by no means infallible. While several drug combinations appeared to be about equally bactericidal in the test tube, only the combination of penicillin plus bacitracin was capable of sterilizing her blood stream. Because of the patient's desperate condition the effect of vancomycin used alone was not explored. Thus it remains uncertain whether this drug, alone or in combination, contributed materially to her cure. The failure of ristocetin to exert any significant antibacterial effect in vivo, in spite of marked in vitro activity against the organism, has also been experienced in other cases of staphylococcal endocarditis (Rantz and Jawetz, to be published). The role of penicillin in this patient's treatment deserves special comment. Her organism regularly was inhibited only slightly and temporarily by penicillin, 50 units per milliliter, and obviously produced penicillinase. Doses of 40,000,000 units daily, given together with other inhibitory drugs, such as novobiocin or chloramphenicol, failed to sterilize the blood stream. Similarly, bacitracin together with these agents was ineffective. Only when penicillin and bacitracin were administered simultaneously did blood cultures remain sterile. Thus the laboratory test provided useful information in pointing to the pair penicillin-bacitracin in spite of marked penicillin resistance of the Staphylococcus; yet the test failed to distinguish between this drug pair and others which were effective in vitro but failed in the clinical test.

CASE 5.§—A 44-year-old white man entered the hospital on March 30, 1956, for a mitral valvulotomy.

At age 7 years he had suffered from acute rheumatic fever. He had recurrences of active rheumatic fever almost every year until he was 19 years old but was asymptomatic subsequently. One year ago he developed exertional and nocturnal dsypnea, orthopnea, and hemoptysis and had to stop work as a laborer.

Physical examination showed a somewhat debilitated dyspneic man. The blood pressure was 115 systolic and 85 diastolic. The cardiac findings showed auricular fibrillation and severe mitral stenosis, with cardiomegaly and beginning decompensation.

The patient was digitalized and placed on a low-salt diet. Additional studies confirmed the presence of a very marked mitral stenosis, and the patient appeared to be a good candidate for mitral valvulotomy. Laboratory examination of blood and urine were within normal limits.

On April 4 mitral valvulotomy was performed with penicillin "prophylaxis." The mitral valve was found to be tightly stenosed and calcified, and a regurgitation jet was also present. Some degree of aortic stenosis was found. The mitral valve was finger-fractured to give a 2 cm. opening. The immediate postoperative condition of the patient was satisfactory. However, on the first postoperative day there was fever, with temperature of 103.1 F (39.5 C) and chest pain, and the next day

§ Reported with permission of Dr. Dace Mitchell.

pleuropericarditis developed. Cultures of the blood and pericardial fluid yielded large numbers of hemolytic S. pyogenes var. aureus, coagulase positive.

Antibiotic sensitivity determinations of this organism gave the following results: It was inhibited moderately well by bacitracin, 1 unit per milliliter; chloramphenicol, 10μg., or erythromycin, 2μg. It was inhibited only transiently by streptomycin, 20μg. per milliliter; tetracycline, 10μg., or novobiocin, 4μg., and not inhibited at all by penicillin, 10μg., or neomycin 2μg.

The following drug combinations were both completely inhibitory and fairly rapidly bactericidal (amounts per milliliter):

Bacitracin 1 unit + chloramphenicol 20μg.
Bacitracin 1 unit + erythromycin 2μg.
Bacitracin 1 unit + streptomycin 20μg.

A number of other combinations had less marked effects.

On the basis of these findings, the patient was treated with bacitracin, erythromycin, and chloramphenicol, as shown in Chart 3. For some days he ran a stormy course, was markedly disoriented, and showed evidence of septic chorioretinitis. The presence of other metastatic abscesses seemed probable. However, the blood cultures were negative, and treatment was discontinued after three weeks of constant physical improvement but semipsychotic behavior. During subsequent weeks his mental status improved, and he appeared well enough to be discharged on June 7, 1956.

A few days later he was readmitted, acutely ill, with a septic fever and blood cultures positive for the same Staphylococcus, with identical in vitro behavior to antibiotics. Accordingly he was retreated for four weeks with the same drug combination and showed a rapid uneventful response. Follow-up examinations for the next 18 months indicated cure of the infection and a satisfactory postoperative response to the valvulotomy.

Comment: The relapse in this patient probably can be attributed to insufficient duration of therapy, necessitated by his psychotic behavior. It is probable that either the endocarditis was not eradicated by the first course of treatment or bacteria survived in other abscesses and were disseminated from such a focus. In the second course of treatment, the drugs selected by laboratory test (bacitracin, chloramphenicol, and erythromycin) were employed for four weeks and resulted in permanent cure. Penicillin was employed during the first course of treatment because the overwhelming illness made recovery so unlikely that some physicians felt unable to resist the recom-

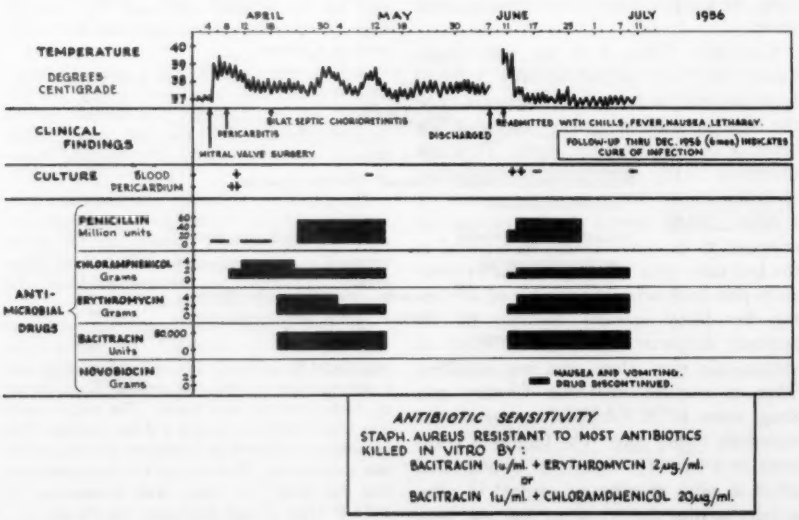

Chart 3.—Clinical course of Case 5. Staphylococcus sepsis with pericarditis, endocarditis, and chorioretinitis following mitral valvulotomy.

mendation in the literature [8] to employ this drug, in spite of apparent resistance of the organism in vitro. It is not possible to determine the role that penicillin may have played in curing the patient, but this drug was given for only two weeks during the second, curative, course of therapy and may have contributed nothing at all.

Staphylococcal Pneumonia and Empyema

A recent authoritative review of staphylococcal pneumonia reported a mortality rate of 67%,[9] emphasizing the extreme severity of such infections. The three patients treated during the period of this report for staphylococcal pneumonia had an exceedingly stormy course but survived. All three acquired the drug-resistant Staphylococcus infection in the course of surgery in hospitals. In at least one of them (Case 6) the blame for this infection can be placed on the misguided use of tetracycline for "prophylaxis" in a clean elective surgical procedure.

CASE 6.‖—A 58-year-old white man entered the hospital on Sept. 16, 1957, for the repair of an inguinal hernia (Chart 4).

Bilateral herniorrhaphies had been performed six years earlier, without difficulty. At that time a diagnosis of Parkinsonism was also made. Six weeks ago, while pushing a lawnmower, the patient suddenly felt pain in the right flank, radiating into the groin and down the right thigh. Recurrence of a right inguinal hernia was diagnosed in the clinic, and he was scheduled for its surgical repair.

Physical examination on admission showed a healthy-looking man with normal temperature and pulse rate. The blood pressure was 135 systolic and 70 diastolic. The face was inexpressive but not mask-like. There was minimal tremor of the extremities and no definite rigidity. A right direct inguinal uncomplicated hernia was present.

Examination of the blood showed a hemoglobin of 15 gm. per 100 ml. and a white blood cell count of 6,200, with a differential count of 52% polymorphonuclear leukocytes, 43% lymphocytes, and 4% monocytes. The urine was entirely normal.

The surgical repair of the right inguinal hernia, on Sept. 17, was quite uneventful. The structures were of good quality, and the entire procedure was brief. Upon his leaving the operating room, tetracycline, 2 gm. daily was ordered. The postoperative course seemed uneventful for three days, but on the fourth day (Sept. 21) occurred nausea, vomiting, and diarrhea. A smear of the stool indicated the presence of a moderate number of staphylococci among the usual enteric flora. The tetracycline administration was immediately stopped.

On the fifth postoperative day (Sept. 22) (Chart 4) the temperature rose to 104. F, there was some right chest pain, and pneumonitis of the right midlung field was demonstrated by physical and x-ray examination. Chloramphenicol, 2 gm. daily, was started, and the temperature rapidly fell to near 100.4 F (38 C). However, the white blood cell count kept rising and on Sept. 25 reached 29,000, with 90% polymorphonuclear cells. On that

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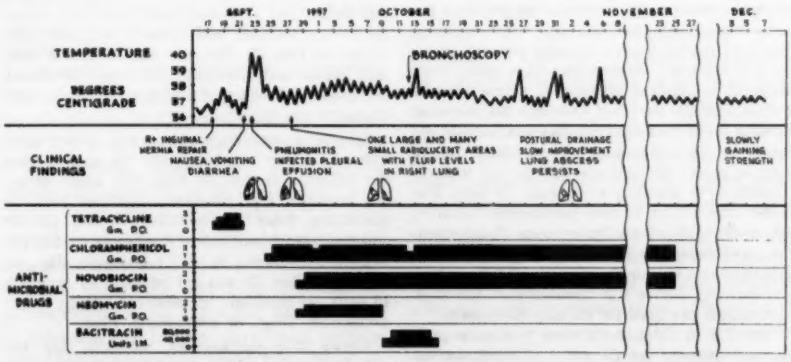

Chart 4.—Clinical course of Case 6. Staphylococcal pneumonia and lung abscesses following antibiotic prophylaxis. Gm. Po under Neomycin should read Gm. I. M.

day thoracentesis yielded 40 ml. of serosanguinous fluid, which yielded large numbers of hemolytic S. pyogenes var. aureus on culture. The patient had a moderate cough but appeared very toxic. On Sept. 27 he became delirious and went into shock, with blood pressure readings of 95 systolic and 60 diastolic. X-ray examination of his chest showed multiple translucent areas, some with fluid levels, probably representing abscesses, in the right middle and lower lung fields. The nonprotein nitrogen was 85 mg. per 100 ml. of blood. Blood cultures showed no growth.

Antibiotic sensitivity determinations on the Staphylococcus recovered from pleural fluid and sputum gave the following results. In tests with single drugs, the organism was completely inhibited by bacitracin, 1 unit per milliliter, but was not significantly affected by penicillin, 10 units; streptomycin, 20μg.; chloramphenicol, 20μg.; tetracycline, 10μg.; novobiocin, 6μg., neomycin, 2μg.

The following antibiotic combinations were both completely inhibitory and rapidly bactericidal in vitro (amounts per milliliter):

Neomycin 2μg. + chloramphenicol 20μg.
Neomycin 2μg. + erythromycin 2μg.
Neomycin 2μg. + novobiocin 6μg.
Bacitracin 1 unit + chloramphenicol 20μg.
Bacitracin 1 unit + erythromycin 2μg.

A number of other combinations had less pronounced effect.

Novobiocin and neomycin were added to chloramphenicol on Sept. 27, and the patient slowly began to improve. The subsequent course is depicted in Chart 4. As the patient was unable to expectorate well, attempts were made to aspirate some of the evidently necrotic material by bronchoscopy. This met with only limited success. The sputum continued to show diminishing numbers of hemolytic staphylococci. Frequent x-ray examinations indicated resolution of the pneumonic process in some areas, but the translucencies persisted for many weeks and filled in only very gradually. When the patient became stronger postural drainage was instituted. Intermittent fever spikes were attributed to impaired drainage. Contrast material injected through the chest wall into the abscesses appeared in the bronchial tree and was coughed up. Because of the widespread "honeycombing" of the right lung and the patient's debility the thoracic surgeons were unwilling to operate. In early November the patient became permanently afebrile, and on Nov. 25 all antibiotics were discontinued. After continuing slow improvement, the patient was discharged to outpatient care in mid-December, with the lung abscess still demonstrable. His slow improvement continued for the next five months.

CASE 7.¶—A 75-year-old man had undergone chemopallidectomy for the relief of Parkinsonism in March, 1957. During his convalescence from this operation the patient fell and fractured the left hip. A Smith-Petersen nail was inserted, and the patient was discharged home on June 29, 1957. In subsequent months he suffered from increasing pain in the hip. On Oct. 7, 1957, he was readmitted to the hospital for a revision of the previous orthopedic repair.

Physical examination on admission showed a chronically ill old man, with marked tremor, some rigidity, and poor speech. His temperature, pulse, and respiration were normal, and the blood pressure was 112 systolic and 65 diastolic. Movement of the left hip was very limited and exceedingly painful. The patient had urinary incontinence. For this reason an indwelling catheter was inserted, and the patient was given sulfisoxazole, 2 gm. daily. Examination of blood and urine were within normal limits.

A hip arthroplasty was performed on Oct. 12. The joint was open for 45 minutes during the operation. Therefore, chloramphenicol, 2 gm. daily, was begun immediately for "prophylaxis." On the second postoperative day the patient had some chest pain and fever, with temperature up to 104.0 F. (Chart 5). There was increasing cough, but on the next day a chest x-ray was within normal limits. For the next few days the patient appeared increasingly ill and lethargic, with swinging fever (temperature to 39 C), cough, and poor intake of fluid and food. On Oct. 22 there was fever (temperature over 104.0 F); coarse rhonchi were heard for the first time; the white blood cell count was 20,800, with 80% polymorphonuclear leukocytes, and chest x-rays indicated the presence of bilateral pneumonitis. Chloramphenicol was stopped, and penicillin plus streptomycin, started. However, hemolytic S. pyogenes var. aureus grew out as the predominant organism in sputum cultures. Blood culture remained negative. Increasing laryngeal obstruction and very inadequate ventilation necessitated tracheostomy and frequent bronchial aspirations on Oct. 23. The next day the patient went into shock and auricular fibrillation developed. He was digitalized and placed on antistaphylococcal chemotherapy (Chart 5).

Sensitivity determinations on the staphylococci isolated in large numbers from the sputum gave the following results: In tests with single drugs, the organism was completely inhibited only by novobiocin, 0.4μg. per milliliter. It was slightly and transiently inhibited by bacitracin, 1 unit per milliliter; erythromycin, 2μg.; neomycin, 2μg., or ristocetin, 10μg. It was not inhibited by penicillin 10 units per milliliter; streptomycin, 20μg.; chloramphenicol, 20μg., or tetracycline, 10μg.

Among drug combinations, neomycin, 2μg. per milliliter, plus novobiocin, 4μg. was completely inhibitory and very rapidly bactericidal, and novo-

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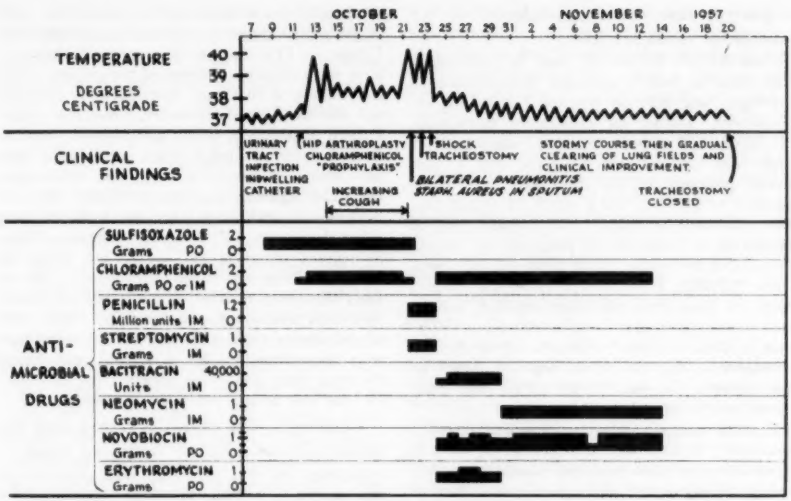
OCTOBER
NOVEMBER
1957
7 9 11 13 15 17 19 21 23 25 27 29 31 2 4 6 8 10 12 14 16 18 20
TEMPERATURE
DEGREES CENTIGRADE
40
39
38
37
CLINICAL FINDINGS
URINARY TRACT INFECTION INDWELLING CATHETER
HIP ARTHROPLASTY CHLORAMPHENICOL "PROPHYLAXIS"
INCREASING COUGH
SHOCK TRACHEOSTOMY
BILATERAL PNEUMONITIS STAPH. AUREUS IN SPUTUM
STORMY COURSE THEN GRADUAL CLEARING OF LUNG FIELDS AND CLINICAL IMPROVEMENT
TRACHEOSTOMY CLOSED
ANTI-MICROBIAL DRUGS
SULFISOXAZOLE Grams PO 2 0
CHLORAMPHENICOL Grams PO or IM 2 0
PENICILLIN Million units IM 1.2 0
STREPTOMYCIN Grams IM 1 0
BACITRACIN Units IM 40000 0
NEOMYCIN Grams IM 1 0
NOVOBIOCIN Grams PO 1 0
ERYTHROMYCIN Grams PO 1 0

Chart 5.—Clinical course of Case 7. Staphylococcal pneumonia following surgical repair of hip fracture in patient with parkinsonism.

biocin, 4μg., per milliliter, plus chloramphenicol, 20μg., was somewhat less so. Other combinations appeared to be appreciably less effective.

The initial response to "antistaphylococcal therapy" was slight. The patient continued to run a very stormy course. His antibiotic regimen was modified on Oct. 30, in accordance with the laboratory results. Subsequently he improved slowly, and became afebrile, and his lung fields cleared gradually. All antimicrobial treatment was discontinued on Nov. 14, and the tracheostomy was closed on Nov. 20. At that time he had recovered to the level of his hospital reentry in October. Still seriously debilitated, he was returned to orthopedic care in December, 1958.

Comment: Case 6 was given tetracycline upon leaving the operating room because of the diagnosis of "Parkinsonism." Apparently the surgeon felt that the patient was in considerable danger from postoperative pulmonary infection, which should be prevented by "antibiotic prophylaxis." As described so well by Howe [10] and others, this procedure only led to the selection of drug-resistant organisms and their implantation in respiratory and intestinal tracts. Had a pulmonary infection developed without "chemoprophylaxis" it could have been effectively and simply treated with specific drugs. This patient's infection, however, was caused by a resistant Staphylococcus, undoubtedly derived from the hospital environment, which required very protracted treatment with toxic drugs. It appears probable that the patient survived only because of the very intensive antimicrobial therapy, but there is no proof that drugs other than those selected on laboratory evidence might not have succeeded equally well.

Case 7 had unequivocal severe Parkinsonism. He received antimicrobial "prophylaxis," not to prevent pulmonary complications but because of an indwelling catheter and because the hip joint was open for 45 minutes during the surgical procedure. This patient's staphylococcal pneumonia unfortunately was not recognized promptly enough to permit effective early treatment. It is very surprising that the several toxic drugs necessary for treatment were tolerated in spite of old age, nephrosclerosis, and impaired renal function and that, after appearing moribund a number of times, the patient could survive the infection. It is highly probable, but again

unproven, that the drugs selected in the laboratory saved his life.

CASE 8.#—A 44-year-old man in good health was found to have a persistent round shadow in his right lung field on repeated radiological examinations. During an exploratory thoractomy, on Jan. 9, 1957, a leiomyomatous hamartoma (benign) was removed from the right lung. On the second postoperative day there was fever (temperature to 102.2 F), and a sample of pleural fluid was submitted for culture. After many days of incubation, a hemolytic S. pyogenes var. aureus grew from the culture. Upon treatment with penicillin, 1,200,000 units, and streptomycin, 1 gm., daily for three days, the fever subsided, and the patient was discharged home to convalesce. However, at home his fever continued, and on the 10th postoperative day the patient began to cough up foul sputum. On Jan. 31, the patient was readmitted to the hospital.

Physical examination on readmission showed a moderately ill man, with a temperture of 100.4 F, complaining of chest pain and raising some foul sputum. X-ray examination of the chest showed an air-fluid level in the dorsal segment of the right lung, where the tumor had been removed. Bronchoscopy was within normal limits. A catheter was inserted through the chest wall to drain the lung abscess, but the temperature rose steadily in spite of the administration of tetracycline and penicillin. Finally, on Feb. 14, open drainage of the lung abscess was instituted. Cultures of the sputum, blood, and abscess at that time revealed a S. pyogenes var. aureus (coagulase-positive, hemolytic, phage Pattern 52/42B/81), which was resistant in vitro to most single antibiotics except bacitracin, 2 units per milliliter; neomycin, 2μg., or novobiocin, 4μg. The organism was rapidly killed in vitro by mixtures of novobiocin, 0.4μg. per milliliter, with either bacitracin, 0.2 units, or neomycin, 0.2μg. Subsequent treatment and course are shown in Chart 6. There was rapid improvement; cultures from all sources remained negative, and the wound was clean and slowly granulated in. There were no significant toxic side-effects. The antibiotics were discontinued on March 7, 1957, and during the next three months the patient fully recovered. He was well at last follow-up, in August, 1957.

Comment: The patient's course and the nature of the infecting organism make it apparent that this infection was acquired in the hospital. The lack of response to open drainage of the lung abscess and the continuing deterioration of the patient's condition on tetracycline administration strongly suggest that the sudden dramatic improvement and ultimate cure in this pa-

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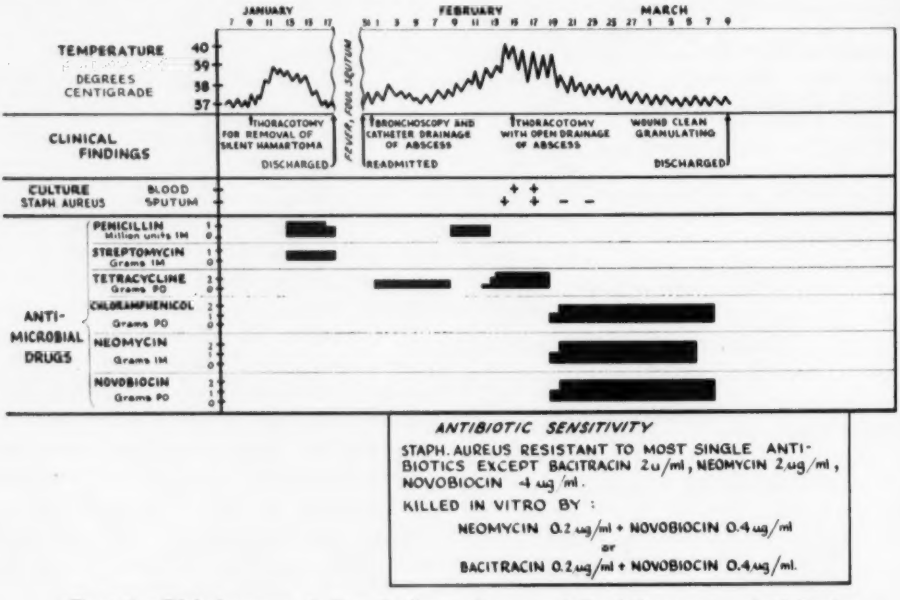

Chart 6.—Clinical course of Case 8. Lung abscess and Staphylococcus sepsis following thoracotomy.

tient probably were a function of the drug combination selected by laboratory test. Conversely, it is not proven that a similar success might not have followed treatment with a single drug, such as novobiocin.

Staphylococcal Osteomyelitis and Septic Arthritis

Two cases of acute osteomyelitis with positive blood cultures in children seen during the period of this report were caused by penicillin-sensitive staphylococci and responded well to that drug. They are not described here. In the two patients with osteomyelitis of the spine, reported below, the drug-resistant staphylococci almost certainly were introduced in the course of transurethral resections. In keeping with the finding of Schirger et al.,[11] the largest number of micrococcal bacteremias in surgical patients follows this procedure. In the third patient, the infectious organism undoubtedly entered the joint at the time of surgery and established itself in spite of so-called "antibiotic prophylaxis."

CASE 9.*—A 60-year-old man developed symptoms of lower urinary tract obstruction attributable to prostatic hypertrophy. A transurethral resection was carried out on March 5, 1956, without difficulty. On the fourth postoperative day the patient suddenly developed a high fever. This subsided after a single intramuscular injection of streptomycin, 1 gm., followed by sulfisoxazole. On March 10, the patient was discharged home and continued to take sulfisoxazole, 1 gm. daily. Four days after discharge, he developed a severe back pain, which was temporarily relieved when he was placed in traction by a physician in another city. However, in mid-April the low back pain became increasingly severe and the back became increasingly stiff. At the same time, there was rising temperature. For these complaints the patient returned to the hospital on April 21, 1956.

On admission, he appeared to be acutely ill and in extreme discomfort, complaining of severe backache. The blood pressure was 150 systolic, 80 diastolic; the temperature was 101.7 F (38.7 C). Physical examination showed marked rigidity of the entire spine and severe spasm of paravertebral muscles but no localized tenderness to percussion over spine or costovertebral angles. The remainder of the physical examination was not contributory. Laboratory examination showed a hemoglobin of 12 gm. per 100 ml., a red blood cell count of 4,400,000 per cubic millimeter, and a white blood cell count of 12,300 per cubic millimeter, with 87% polymorphonuclear leukocytes. The corrected sedimentation rate was 31 mm. in one hour. The urine contained a trace of protein, rare red cells, and occasional white cells. Cultures of urine and blood

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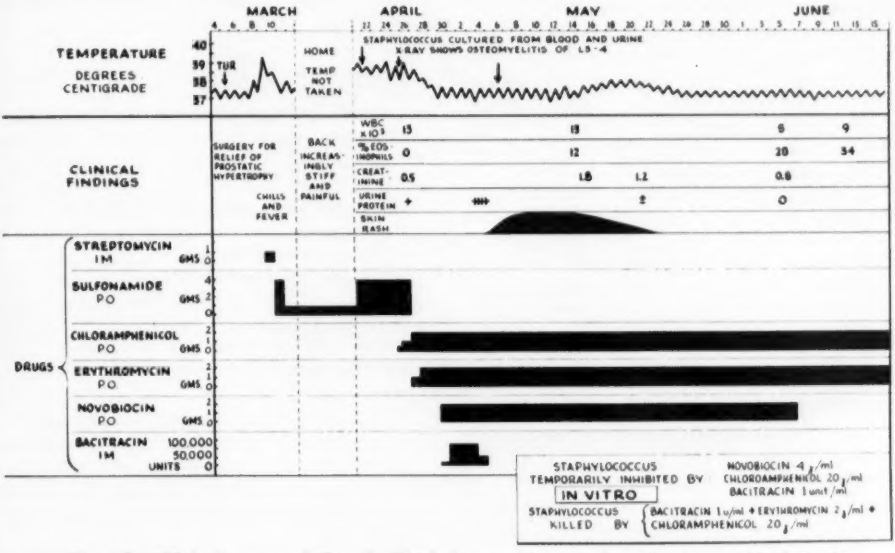

Chart 7.—Clinical course of Case 9. Staphylococcus bacteremia and osteomyelitis following urological surgery.

grew a S. pyogenes var. aureus (coagulase-positive, hemolytic, phage Pattern 7/47/54/77 VA 4), which was not inhibited in vitro by many common antibiotics but was inhibited by novobiocin, 4μg. per milliliter; chloramphenicol, 20μg., or bacitracin, 1 unit. The organism was killed in vitro by bacitracin, 1 unit per milliliter; plus erythromycin, 2μg., plus chloramphenicol, 20μg., and somewhat less efficiently by several combinations containing novobiocin, 4μg.

A spinal fluid examination was within normal limits. Roentgen-ray examination of the spine revealed an osteomyelitis of the fourth lumbar vertebra, with some involvement of the second and third, and marked paravertebral inflammation. The clinical course of the patient and his treatment are depicted in Chart 7. Bacitracin had to be discontinued after four days because of severe proteinuria, hematuria, and sudden nitrogen retention. There were toxic reactions to novobiocin, including troublesome skin rashes and a marked eosinophilia, and so this drug was discontinued after five weeks. These toxic reactions eventually subsided. Chloramphenicol and erythromycin were taken for a total of eight weeks, after which the patient appeared entirely well and roentgenograms of the spine showed beginning improvement. Subsequently, the patient has remained entirely well, and over the period of 14 months the bone structure of lumbar vertebrae has resumed an entirely normal radiological pattern.

CASE 10.†—A 55-year-old white man entered the hospital on Feb. 11, 1957, because of recurrent fever for two months, back pain, and blood cultures positive for S. pyogenes var. aureus.

In March, 1956, the patient presented symptoms of prostatism. Urological examination at that time indicated benign prostatic hypertrophy. In October, 1956, a transurethral resection was performed at another hospital. After two weeks of uneventful convalescence the patient developed fever and symptoms and signs of urinary tract infection. The latter subsided gradually, but a variety of aches and pains appeared referable to extremities and back. In December, 1956, several blood cultures taken during febrile episodes yielded hemolytic S. pyogenes var. aureus. It was assumed that the bacteria originated in the urinary tract, and the patient received a prolonged course of chloramphenicol. Blood cultures in late January, 1957, remained sterile. However, there was intermittent low-grade fever and increasingly severe back pain.

X-ray examination of the back, on Feb. 1, demonstrated a lesion of the right sacroiliac joint and adjoining bone. The area was aspirated and pus obtained, which on culture yielded hemolytic S. pyogenes var. aureus. Other laboratory examinations showed a hemoglobin of 14 gm. per 100 ml., a white blood cell count of 12,000, and a corrected erythrocyte sedimentation rate of 30 mm. in one hour.

Antibiotic sensitivity determinations of the Staphylococcus cultured from the sacroiliac joint yielded the following results: The organism was only slightly and transiently inhibited by bacitracin, 0.2 unit per milliliter; chloramphenicol, 20μg.; neomycin, 2μg., or novobiocin, 4μg. It was not significantly inhibited by penicillin, 10 units per milliliter; streptomycin, 20μg.; tetracycline, 10μg., or erythromycin, 2μg. Vancomycin, 10μg. per milliliter, was strongly inhibitory.

The following drug combinations were both completely inhibitory and rapidly bactericidal (amounts per milliliter):

Bacitracin 1 unit + chloramphenicol 20μg.
Bacitracin 1 unit + erythromycin 2μg.
Bacitracin 1 unit + novobiocin 4μg.

Other combinations had less marked effects.

Combined antimicrobial therapy was begun on Feb. 12, as shown in Chart 8. The infected joint was explored, and infected tissue and bone were removed. The area was packed open, and bacitracin as well as vancomycin was instilled topically. The patient tolerated antimicrobial therapy well, and frequent determinations of serum creatinine showed no continuous rise. As healthy granulation tissue filled the defect the packs were gradually withdrawn. The lesion healed completely; the patient felt well, and follow-up in December, 1957, gave no evidence of recurrence.

CASE 11.‡—A 32-year-old white man entered the hospital on May 17, 1957, for an arthroplasty to correct severe post-traumatic arthritis of the left hip.

Physical examination on admission was entirely unremarkable except for the left hip, which showed markedly limited and painful motion. Laboratory examinations were within normal limits. On May 21, 1957, arthroplasty was performed, with the insertion of a special metallic prosthesis for the left femoral head. Chloramphenicol was administered for "prophylaxis" for four days prior to and more than two weeks after operation.

During the immediate postoperative period the patient felt well and had little pain, although his temperature rose daily to 100.4 F or more. On the eighth postoperative day all drainage had ceased; the wound was well healed, and active exercises were begun.

On June 3, the 13th postoperative day, the patient began to have severe pain in the left hip and a daily fever, with temperature of 100.4 F to 102.2 F. His white blood cell count was 13,500, and his sedimentation rate, 36 mm. in one hour.

† Reported with permission of Dr. Allen Barbour.

‡ Reported with permission of Dr. F. H. Jergesen and Dr. J. H. Bauer.

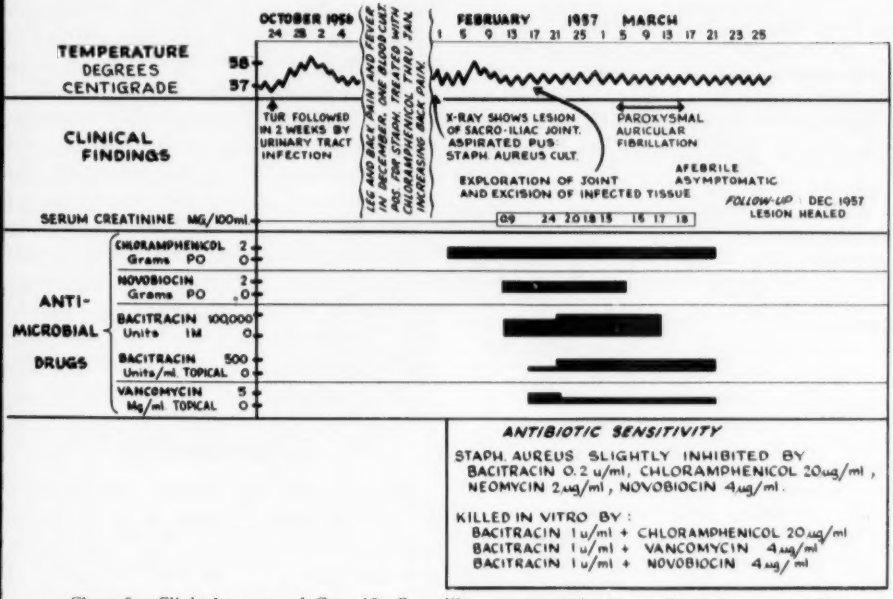
OCTOBER 1956
FEBRUARY 1957 MARCH
TEMPERATURE DEGREES CENTIGRADE
CLINICAL FINDINGS
TUR FOLLOWED IN 2 WEEKS BY URINARY TRACT INFECTION
LEG AND BACK PAIN AND FEVER IN DECEMBER, ONE BLOOD CULT. POS. FOR STAPH. TREATED WITH CHLORAMPHENICOL THRU JAN. INCREASING BACK PAIN.
X-RAY SHOWS LESION OF SACRO-ILIAC JOINT. ASPIRATED PUS: STAPH. AUREUS CULT.
EXPLORATION OF JOINT AND EXCISION OF INFECTED TISSUE
PAROXYSMAL AURICULAR FIBRILLATION
AFEBRILE ASYMPTOMATIC
FOLLOW-UP: DEC 1957 LESION HEALED
SERUM CREATININE MG/100ml
ANTI-MICROBIAL DRUGS
CHLORAMPHENICOL Grams PO
NOVOBIOCIN Grams PO
BACITRACIN Units IM
BACITRACIN Units/ml TOPICAL
VANCOMYCIN Mg/ml TOPICAL
ANTIBIOTIC SENSITIVITY
STAPH. AUREUS SLIGHTLY INHIBITED BY BACITRACIN 0.2 u/ml, CHLORAMPHENICOL 20 ug/ml, NEOMYCIN 2 ug/ml, NOVOBIOCIN 4 ug/ml.
KILLED IN VITRO BY:
BACITRACIN 1 u/ml + CHLORAMPHENICOL 20 ug/ml
BACITRACIN 1 u/ml + VANCOMYCIN 4 ug/ml
BACITRACIN 1 u/ml + NOVOBIOCIN 4 ug/ml

Chart 8.—Clinical course of Case 10. Sacroiliac osteomyelitis due to Staphylococcus following transurethral resection for prostatic hypertrophy.

Exercises were stopped, and the patient was kept at bed rest; but pain and fever persisted, and the hip became tender to palpation. Tetracycline and penicillin were administered. A fluctuant mass developed, which was incised and drained on June 17. Culture yielded hemolytic S. pyogenes var. aureus which, by "disk test," appeared resistant to tetracycline, chloramphenicol, and penicillin but sensitive to erythromycin and streptomycin. Accordingly, systemic therapy was changed to erythromycin (Chart 9) and streptomycin, and later vancomycin was repeatedly instilled into the joint. However,

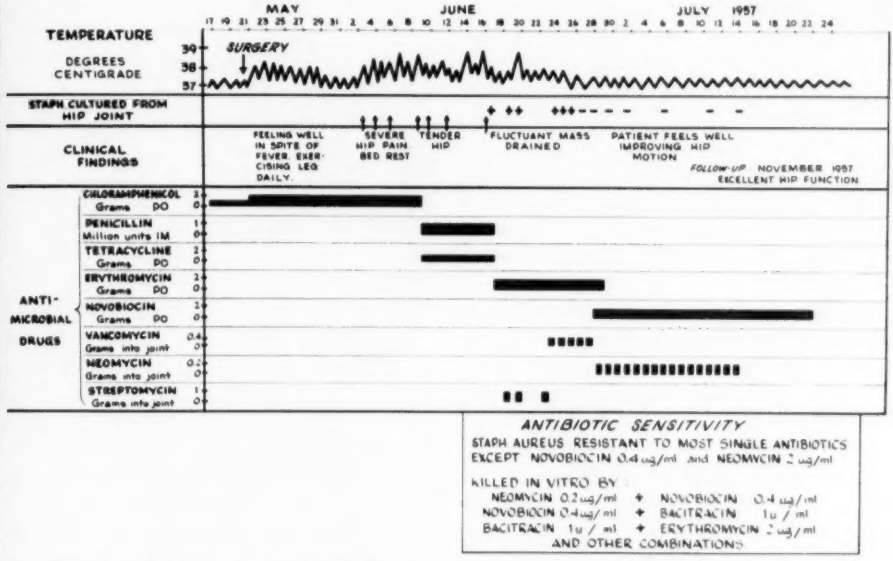
MAY JUNE JULY 1957
TEMPERATURE DEGREES CENTIGRADE
SURGERY
STAPH CULTURED FROM HIP JOINT
CLINICAL FINDINGS
FEELING WELL IN SPITE OF FEVER. EXERCISING LEG DAILY.
SEVERE HIP PAIN BED REST
TENDER HIP
FLUCTUANT MASS DRAINED
PATIENT FEELS WELL IMPROVING HIP MOTION
FOLLOW-UP NOVEMBER 1957 EXCELLENT HIP FUNCTION
ANTI-MICROBIAL DRUGS
CHLORAMPHENICOL Grams PO
PENICILLIN Million units IM
TETRACYCLINE Grams PO
ERYTHROMYCIN Grams PO
NOVOBIOCIN Grams PO
VANCOMYCIN Grams into joint
NEOMYCIN Grams into joint
STREPTOMYCIN Grams into joint
ANTIBIOTIC SENSITIVITY
STAPH AUREUS RESISTANT TO MOST SINGLE ANTIBIOTICS EXCEPT NOVOBIOCIN 0.4 ug/ml and NEOMYCIN 2 ug/ml
KILLED IN VITRO BY:
NEOMYCIN 0.2 ug/ml + NOVOBIOCIN 0.4 ug/ml
NOVOBIOCIN 0.4 ug/ml + BACITRACIN 1 u/ml
BACITRACIN 1 u/ml + ERYTHROMYCIN 2 ug/ml
AND OTHER COMBINATIONS

Chart 9.—Clinical course of Case 11. Staphylococcus joint infection following hip arthroplasty.

cultures from the aspirated joint continued to be positive for the same Staphylococcus.

Antibiotic sensitivity determinations of this organism gave the following results.

It was not inhibited by penicillin, 10 units per milliliter; streptomycin, 20μg., or tetracycline, 10μg., and was only slightly inhibited by erythromycin, 2μg.; chloramphenicol, 20μg.; bacitracin, 1 unit, or vancomycin, 4μg. The organism was completely inhibited and rapidly killed by neomycin, 2μg. per milliliter, or novobiocin, 4μg.

A number of drug combinations were completely inhibitory and rapidly bactericidal; among them were the following combinations (amounts per milliliter):

Neomycin 0.2μg. + novobiocin 0.4μg.
Bacitracin 1 unit + novobiocin 0.4μg.
Bacitracin 1 unit + erythromycin 2μg.
Neomycin 0.2μg. + erythromycin 2μg.

Because of the high bactericidal efficiency of the combination of neomycin and novobiocin the patient was treated with these drugs. Novobiocin, 2 gm., was administered orally, and neomycin, 200 mg., was instilled into the joint cavity daily, as shown in Chart 9. The patient's course was entirely uneventful from that time on, and he recovered completely, without any further local interference. In spite of the presence of the prosthesis in the joint, the infection was eradicated and he gained excellent hip function. Six months later he was entirely well, and his operative result was perfect.

Comment: The striking success of penicillin in curing early osteomyelitis may well be a function of the ability of the drug to kill susceptible staphylococci rapidly. It has been our belief that bactericidal action may be a prerequisite for the effective medical therapy of osteomyelitis, as it undoubtedly is for endocarditis.[2,5] In relatively early bone infection (perferably prior to the appearance of radiological defects) vascularity is sufficient to permit bactericidal drugs or combinations to reach all infected sites and eradicate the micro-organisms. This apparently was true in Case 9. However, when the infection has existed for a longer period and sequestration has occurred systemic chemotherapy without local interference is futile. In conjunction with the debridement of devitalized tissue bactericidal drug action at the site is essential. To circumvent the impairment of blood supply and avoid potential systemic toxicity of drugs like bacitracin or neomycin, we have achieved combined-drug effects by instilling one drug (the more toxic) into the affected area—e. g., joint space, abscess cavity, bone defect—and administering the other drug systemically. This approach was used in Cases 10 and 11. We assume that some diffusion of drug occurs both from the site of the systemic circulation and from the site of topical application. In the tissue where the drugs meet and exert their combined bactericidal effect such action is most needed because persistence of organisms resulting in chronic infection is most probable. Admittedly, we have no proof that events follow this reasoning, but the success in these and other cases is encouraging.

Comment

Infection by drug-resistant staphylococci in hospitals should be prevented rather than treated. However, in spite of fairly intensive efforts to that end, the complexity of factors which promote hospital infection makes it unlikely that satisfactory control will be achieved in many instances. Thus, continued attention will have to be given to effective means of treating these infections, which threaten to nullify many splendid efforts in medical and surgical management of hospitalized patients.

There is no evidence that the basic host-parasite relationship in staphylococcal infection has been altered as a result of the emergence of drug resistance. There is probably no direct increased "virulence" of these organisms except through enhanced host susceptibility.[12] Thus the principles of treatment which have been found valid in preantibiotic days should still apply. In localized processes the application of rest, warmth, and, above all, adequate drainage is as important and effective today as it was 20 years ago (Case 1). A more complex problem is presented by infections which are widely disseminated in patients with impaired host resistance, particularly the elderly, the chronically ill, or the person subjected to major surgical procedures. These people often seem incapable of localizing and eliminating the infectious organisms

through their own defenses, even when bacterial multiplication may be inhibited by antimicrobial drugs. Thus it appears desirable to employ bactericidal drugs or combinations in these situations and to ensure that the drug or drugs reach all sites involved in the infectious process in adequate concentration. Our approach to treatment attempts to utilize these principles.

When dealing with hospital-acquired staphylococcal infections the following points deserve particular mention.

(*a*) There is a sharp dichotomy of opinion regarding the use of penicillin in the treatment of penicillin-resistant staphylococcal infections. Fisher et al.[8] felt that penicillin in massive doses should be used "irrespective of the results of in vitro sensitivity tests." Petersdorf et al.[13] also recommended 20,000,000-40,000,000 units of penicillin daily and stated that over one-half of the staphylococcal strains examined at The Johns Hopkins Hospital were inhibited by 50 units of penicillin in vitro. Conversely, Finland[3] indicated, "I have not found penicillin in any feasible dosage to be of any value alone or when combined with other antibiotics in micrococcic infections when the organism is moderately or highly resistant." Our own experience has been intermediate between these extremes. In a large majority of patients infected with staphylococci which were not inhibited in the test tube by 10 units per milliliter of penicillin (inoculum 10^5 organisms) the administration of that drug alone in doses up to 100,000,000 units daily has not, during the past five years, resulted in eradication of the infection. Occasional transient beneficial effects were readily explained by the fact that in vitro tests often estimate only the highest level of resistance in a microbial population, representing perhaps only very few members of that population. In other words, a given level of penicillin may be able to kill 98% of the staphylococcal population, permitting the growth of only 2%. If complete eradication is necessary for cure then this level of penicillin can be expected to fail, but if temporary suppression of bacteria is sufficient then it might succeed (see below).

On the other hand, we have demonstrated in occasional penicillin-resistant staphylococci definite potentiation of drug action between penicillin and some other agent. Such drug pairs exhibited striking bactericidal activity in vitro, although neither drug alone was significantly inhibitory in the concentration employed. This laboratory result could be applied to some clinical situations, as illustrated in Case 4. This type of combined antibiotic action may be based on the inhibition of penicillinase production by the presence of another drug, as suggested by Chandler.[14] It should be noted that most patients treated by Fisher[8] or Petersdorf[13] received other drugs in addition to large doses of penicillin, and so a similar mode of action could be postulated. In our hands, such a desirable combined-drug effect between penicillin and other agents was observed only infrequently in the laboratory and equally infrequently in patients suffering from infections with penicillinase-producing staphylococci.

(*b*) We have observed the rapid emergence of drug-resistant variants in patients with systemic staphylococcal infection who were treated with erythromycin, streptomycin, or novobiocin alone. We therefore do not employ these drugs singly[3] but use them in combination with a second drug which has probable or proven activity against the infecting organism. In order further to diminish the problem of emerging drug resistance, novobiocin has been restricted since June, 1956, in the University of California Hospitals.[4] It has been administered in the course of two years to only 37 patients with serious staphylococcal infections, and the "hospital staphylococci" of our institution remain sensitive to that drug. Several other hospitals in the area have instituted similar drug restrictions, which almost certainly benefit the community.

(*c*) Because of their toxic potentialities bacitracin and neomycin have been employed only to a very limited extent in medical

practice.[15] As a result, microbial resistance to these drugs has not developed on a large scale. It is generally accepted that they should be employed parenterally with restraint and only after an etiologic diagnosis of infection due to a susceptible microorganism. However, in properly selected cases and in a suitable dose and route, these drugs may be of unique value in staphylococcal infections resistant to the more commonly used and more widely abused antibiotics. The physician must constantly weigh the risks inherent in the use of these drugs in a particular patient against the risk of death because the drug was not employed to control infection.

With familiarity these admittedly toxic agents lose some of their terror. Thus one becomes accustomed to the proteinuria and hematuria, which regularly occur during bacitracin treatment, in the knowledge that these disappear soon after the drug is discontinued and at times even sooner. Conversely, one becomes alert to any rise in nitrogen retention in patients receiving bacitracin, because this sign often heralds more serious nephrotoxicity. We have employed bacitracin and neomycin only when laboratory results indicated resistance of the staphylococci to other, less toxic, antibiotics and susceptibility to these toxic drugs either alone or more commonly in combination with other drugs.

Sometimes it is possible to obtain the benefit of bacitracin or neomycin in combination with other agents without the risk of toxicity. This can be accomplished by introducing bacitracin or neomycin topically, in relatively high concentration, into a joint, abscess cavity, or pleural space and administering the other member of the desirable drug pair systemically (Cases 10 and 11). Bacitracin and neomycin diffuse to a certain extent into the limiting structure and there meet the systemically distributed other antibiotic, resulting in the desired combined effect in those tissues where infection is particularly difficult to eradicate. Yet the systemic levels of bacitracin or neomycin remain too low to give rise to significant toxic side-effects.

(*d*) Most investigators agree that in the treatment of serious systemic infections by drug-resistant staphylococci treatment with two or more drugs is mandatory. There is, however, no agreement as to the optimal method of selecting such drug combinations. Undoubtedly, recent experience with the treatment of similar infection in a given hospital will influence the selection. This initial selection of several drugs is of vital importance for prompt treatment, a most urgent requirement for optimal response. This initial drug selection is subsequently modified according to the results of laboratory tests.

The ability of various single drugs to inhibit the etiologic organism in vitro as revealed by the "disk test" can often serve as a guide. In addition, we feel strongly that a test which evaluates the effect of drug combinations on a bacterial population can be of great assistance. The test employed in our laboratory estimates semiquantitatively both prolonged inhibition of growth and bactericidal effects. In some instances the results of this test only confirm the selection of drugs on the basis of "disk tests," i. e., the combined effect appears to be only a summation of apparent single-drug effects (e. g., Case 9). In other instances, however, the combined-antibiotic sensitivity test yields information beyond that obtainable by tests with single drugs.[4-6,16,17] In particular it indicates whether one drug might markedly enhance the bactericidal effect of another or whether it might delay the emergence of variants resistant to the other drug. Extensive experiments reviewed elsewhere [5] have proved that either of these effects can occur with a drug concentration far below that which has definite antibacterial action by itself. Some of the cases presented in this report, particularly Cases 3, 4, 6, 8, and 11, indicate that repeated selection of drugs by "disk test" failed, whereas the combined-antibiotic sensitivity test revealed information which

led to cure. Admittedly, the results of any combined-antibiotic sensitivity test must be judiciously interpreted and integrated with clinical experience. This test does not lend itself to a "routine laboratory" but can be very valuable in qualified hands.

Summary

Serious infections caused by antibiotic-resistant staphylococci currently present an outstanding challenge to antimicrobial therapy. While many localized infections of soft tissues respond well to conventional management, including rest, drainage, and bacteriostatic drugs, this is not the case with other forms of involvement, particularly endocarditis, osteomyelitis, or pneumonia caused by such staphylococci. Our approach to the selection of bactericidal antibiotic combinations for the treatment of such cases is illustrated by means of 11 representative patients seen in 20 months during 1956-1957. Some factors which probably contribute to the successful management of these serious staphylococcal infections are discussed.

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The material presented here appeared as a Scientific Exhibit at the 43d Annual Meeting of the Radiological Society of North America, Chicago, November, 1957. While it was not written primarily as a "review" paper its appearance in this section seems appropriate, since it presents conclusions and opinions drawn from an extensive list of up-to-date references on the subject.

P. S. R.

A Primer on Radiation Hazards for Physicians

RICHARD E. PETERSON, M.D.; JULIUS G. BARON, M.D.; BARTIS M. KENT, M.D., and TITUS C. EVANS, Ph.D., Iowa City

It should be emphasized that this presentation is intended to be instructional and is subject to the limitations of present available knowledge. Attempts have been made to quote authorities, but there is no intention to submit this as a handbook or authoritative guide.

Radiation Units and Equivalents *

Roentgen (r).—The exposure (x-rays or γ-rays) causing in 1 cc. of air, under standard conditions, production of positive and negative ions, either kind of them having altogether the charge of one electrostatic unit. The *roentgen* is a purely physical unit and has no direct relation to absorption or biological effect of radiation.

Roentgen Equivalent Physical (rep).—Obsolete. Exposures of any kind of radiation resulting in ionization equivalent to 83 ergs per gram of air or 93 ergs per gram of tissue.

Radiation Absorbed Dose (rad).—The radiation energy absorbed by a small volume of tissue divided by this volume. Its unit is 100 ergs per gram, called rad.

Integral Dose (gm.-r or gm.-rad).—The total energy absorbed by all the tissues throughout the irradiated volume. It has been calculated in gram roentgens and may be in gram-rads.

Rad Equivalent Man (rem).—The rad, multiplied by the biological effectiveness of a particular quality of radiation, relative to that of conventional x-radiation.

Sources of Radiation

Occupational Hazards.[1-5]—As of 1951, a total of 125,000 x-ray units was used in the healing arts in the United States. Operating personnel potentially exposed were estimated at more than 215,000. To this should be added personnel in industrial radiography and in mining and concentrating radioactive ore, plus construction and operating personnel for nuclear reactors and particle accelerators. In the absence of specific data, the total occupational (potentially exposed) population is estimated to be at least 225,000.

On the average, less than 0.5% of the weekly exposures of hospital x-ray personnel are greater than 0.3 r (15 r per year). At least one hospital has reported that its personnel averaged less than 1/10 of this level of radiation (0.03 r per week, or 1.5 r per year). This latter figure could also be stated as 105,000 gm.-r per year

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*Units are given in general terms for the nonspecialist. For exact terminology, consult National Bureau of Standards Handbook 62, Report of International Committee on Radiation Units and Measurements, 1957.

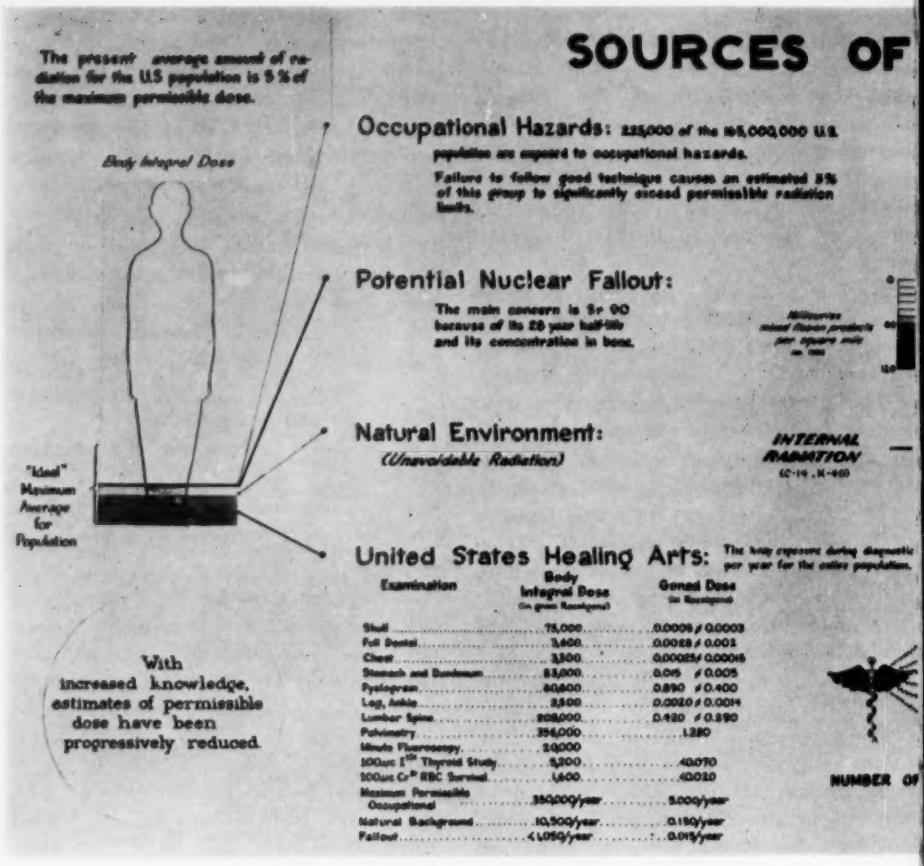
(10× background). On the other hand, when one considers, for example, that over one-half of California's general practitioners (or one-fourth of all California physicians) do their own x-ray work, the outlook is more ominous. Some physicians may have had inadequate training in radiation protection and use of x-ray equipment; this may considerably increase their exposure.

Nuclear Fall-Out.—This is discussed only in terms of hazards resulting several hundred or more miles distant from nuclear explosions.[6,7]

The fission process results in a wide variety of radioactive elements being shot up into the atmosphere and later returning to earth after dispersal by wind, rain, etc. Sr^{90}, Cs^{137}, and I^{131} are commonly reported in fall-out. The resulting hazards depend upon the half-lives of the radioactive species and the likelihood of biologic incorporation. Measurable increases in the radioactivity of a wide variety of human food stuffs have been noted since 1950. Anderson [8] estimated the 1956 average intake of Cs^{137} as 1.5 mμc. per month, which results in about 1/20th of the radiation received from K^{40}, or 1% of all natural radiation. The I^{131} content of thyroids in animals slaughtered is clearly increased, but human consumption of significant amounts of animal thyroids is not likely.[9,11] I^{131} has been inhaled in measurable tracer quantities by humans on at least one occasion after Nevada test explosions.[10] Co^{60} has recently been reported concentrated in clams.[12] However, these do not constitute the main fall-out hazards.

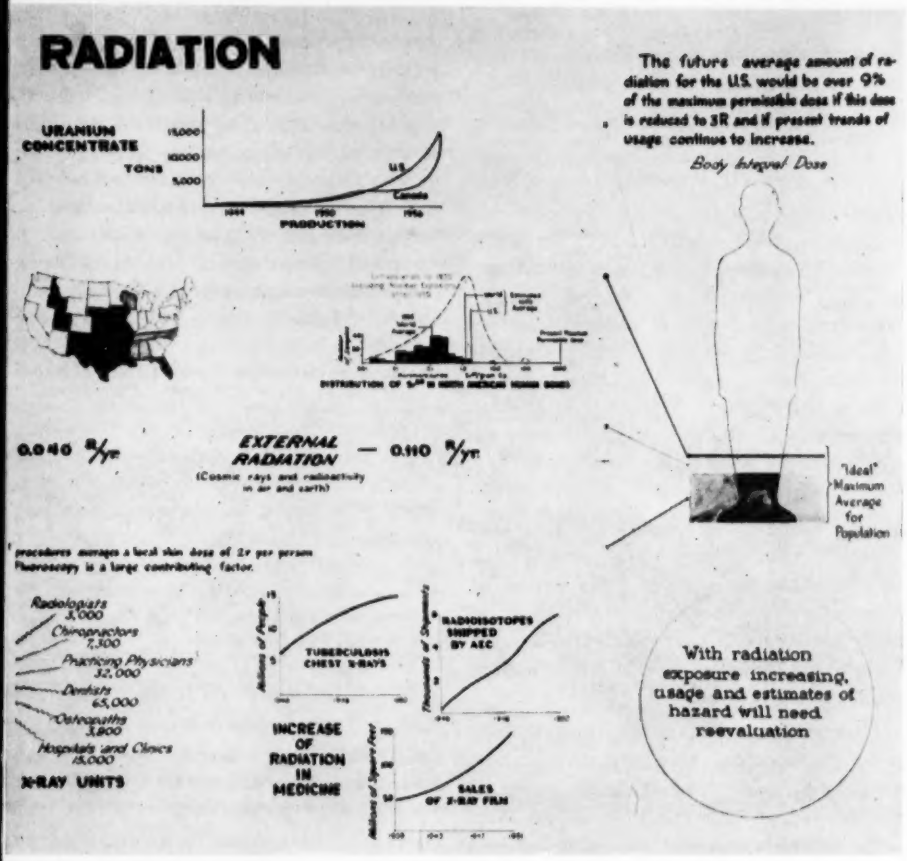
Because of its 28-year half-life and its biologic similarity to calcium, Sr^{90} is an increasingly serious problem in terms of bone irradiation.[13] From the analyses of the Sr^{90} contents of about 500 autopsy samples of human bones obtained from 17 stations in a world-wide network, Kulp, Eckelmann, and Schulert [14] have presented data on the present Sr^{90} burden from fall-out. They conclude that the present world-wide average content of Sr^{90} in man is about 0.12μμc. per gram of calcium. Of the 199 cases from North America, 89% fell within a factor of 10 of the average. The average value is 1/10,000 of the presently accepted maximum permissible concentration (MPC) for occupational exposure, 1/100 of the concentration at which the British Medical Council suggested "the need for immediate consideration of the problem." The MPC for Sr^{90} was determined by comparison with data for radium. It has recently been suggested that the MPC for radium (0.1μg.) may need revision to a lower quantity.[15] Although the average values for Sr^{90} in human bones from different continents showed no marked variations beyond the expected lower values for the southern hemisphere, a definite age effect was observed. Young children have three to four times more Sr^{90} per gram of calcium than adults.[16]

The measured average Sr^{90} content is in very good agreement with a predicted value based on fall-out measurements and discrimination factors in the soil-plant-milk-human chain. Carrying the prediction further, Kulp, Eckelmann and Schulert [14] estimate that in 1970, as a result of the 50 megatons of fission *exploded prior to 1957*, the average body burden in the United States will be about 2μμc. of Sr^{90} per gram of calcium, while the average world-wide concentration will reach about 1.3μμc. Furthermore, according to an Associated Press report of a press conference held in New York on Feb. 7, 1957, Kulp, Eckelmann, and Schulert [14] estimate that, if tests *continue at their present rate*, the average world-wide concentration will be 4μμc. to 8μμc. of Sr^{90} per gram of calcium by 1970. Their upper figure would correspond to only 1/125 of the presently accepted MPC but would approach the level considered significant by the British Medical Council, although our present data indicate that it is unlikely for many people to exceed these averages by more than a factor of 10. The problem of individual variation is important, and detailed studies on probable maximum concentration are being made. Studies are


The present average amount of radiation for the U.S population is 5 % of the maximum permissible dose.
Body Integral Dose
"Ideal" Maximum Average for Population
With increased knowledge, estimates of permissible dose have been progressively reduced.
SOURCES OF
Occupational Hazards: 225,000 of the 165,000,000 U.S. population are exposed to occupational hazards.
Failure to follow good technique causes an estimated 5% of this group to significantly exceed permissible radiation limits.
Potential Nuclear Fallout:
The main concern is Sr 90 because of its 28 year half-life and its concentration in bone.
Natural Environment:
(Unavoidable Radiation)
INTERNAL RADIATION
United States Healing Arts:
Examination
Body Integral Dose
Gonad Dose
Skull 75,000 0.0008 / 0.0003
Full Dental 3,600 0.0028 / 0.001
Chest 3,500 0.00025 / 0.00015
Stomach and Duodenum 85,000 0.015 / 0.005
Pyelogram 60,600 0.890 / 0.400
Leg, Ankle 2,500 0.0020 / 0.0014
Lumbar Spine 208,000 0.420 / 0.280
Pelvimetry 294,000 1.280
Minute Fluoroscopy 20,000
100μc I131 Thyroid Study 5,300 40.070
100μc Cr51 RBC Survival 1,600 40.020
Maximum Permissible Occupational 350,000/year 5,000/year
Natural Background 10,500/year 0.150/year
Fallout <1,050/year 0.015/year
NUMBER OF

also under way to devise treatments to mobilize Sr^{90} from the body after it has been ingested. The increase in γ-radiation background from fall-out [18,19] is estimated to average less than 10% of previous background, or less than 1,000 gm.-r per year to the population. Similar effects could be brought about by fission products from possible accidents in industrial or nuclear power reactors.

Natural Radiation Background.—The *internal dose* (from K^{40}, C^{14}, and radium) is probably fairly stable over the earth except for variations in radium content and more recently Sr^{90}. The *external dose* varies with the type of earth surface, the surrounding wall material, the altitude, etc. Cosmic-ray intensity increases with altitude and distance from the equator. The level of γ-radioactivity in the earth's surface varies by a factor of 3 from that over the ocean to over ordinary granite. The manner in which these variations occur is illustrated by data collected by W. F. Libby.[21] The external dose of 0.10 r per year is only an average, and some parts of the United States range up to four times higher. If one spent an entire year in a uranium mine with ore of minimum AEC-acceptable content of 0.1%, the radiation dose would be at least 50 times the average cited. In Travancore, India, the beaches of the monazite areas have γ-background doses ranging from 0.2 to 2.6 r per year. The biologic consequences of such radiation have not yet been studied.[22]


RADIATION
The future average amount of radiation for the U.S. would be over 9% of the maximum permissible dose if this dose is reduced to 3R and if present trends of usage continue to increase.
Body Integral Dose
URANIUM CONCENTRATE
TONS
U.S.
Canada
PRODUCTION
0.040 R/yr.
EXTERNAL RADIATION
(Cosmic rays and radioactivity in air and earth)
— 0.110 R/yr.
"Ideal" Maximum Average for Population
procedures averages a local skin dose of 2r per person
fluoroscopy is a large contributing factor.
Radiologists 3,000
Chiropractors 7,300
Practicing Physicians 32,000
Dentists 65,000
Osteopaths 3,800
Hospitals and Clinics 15,000
X-RAY UNITS
TUBERCULOSIS CHEST X-RAYS
RADIOISOTOPES SHIPPED BY AEC
INCREASE OF RADIATION IN MEDICINE
SALES OF X-RAY FILM
With radiation exposure increasing, usage and estimates of hazard will need reevaluation

Taking an average sum for internal and external natural background radiation of 0.150 r and assuming an average body weight of 70 kg., a whole-body integral-dose estimate of 10,000 gm.-r per person per year results. The more refined estimate shown in Table 2 is from the Report of the United Nations Scientific Committee on the Effects of Atomic Radiation.[20]

Medical Usage of Diagnostic X-Rays.—Irradiation exposure from occupation, nuclear fall-out, and natural background can be assumed to be whole-body exposure because these radiations are of high energy and originate from diffuse sources. Back-

TABLE 1.—*An Estimate of Radiation Dose from Fall-out*[20]

	Gonad Dose	Osteocyte Dose	Integral Marrow Dose	Whole-Body Integral Dose
30-yr. external contribution from fission products produced up to 1957	0.5–10 mrem	0.5–10 mrem	1–15 gm.-rem	35–700 gm.-rem
Internal contribution from present Cs^{137} human burden	1 mrem/yr.		1.5 Gm.-rem/yr.	70 gm.-rem/yr.
Contribution from Sr^{90} (*a*) Present		1–5 mrem/yr.	0.5–1.5 gm.-rem/yr.	20 gm.-rem/yr.
(*b*) In 1970 if tests are stopped by end of 1957		6–30 mrem/yr.	3–9 gm.-rem/yr.	120 gm.-rem/yr.
(*c*) In equilibrium if tests continue at the present rate		80–400 mrem/yr.	40–120 gm.-rem/yr.	1,600 gm.-rem/yr.

TABLE 2.—*Estimated Annual Background Dose Rate*[22]

Source	Gonad Dose, Mrem/Yr.	Osteocyte Dose, Mrem/Yr.	Whole-body Integral Dose, Gm.-rad/Yr.	Integral Marrow Dose, Gm.-rad/Yr.
External				
Cosmic rays	25-37	25-37	1,750-2,590	37-55
Terrestrial radiation	40-60	40-60	2,800-4,200	60-90
Atmospheric radiation	1	1	70	1.5
Internal				
K^{40}	20	5	1,400	?
C^{14}	1-2	1-2	70-140	1.5-3
Rn-Th	2		140	3
Ra		15-70		0.5-5
Approximate totals	100	120	7,000	160?

ground radiation is *roughly constant* over almost the whole world, and mankind has been exposed to it beyond the period of human history. This minimum radiation is easily measurable. Consequently, the average background radiation should be the "natural standard of reference." [23]

However, for exposures in diagnostic x-ray examinations, this comparison cannot always be readily made. The main reason for this is that these examinations are done with relatively low-energy radiation and only small portions of the body are exposed. There are experimental data showing that the same exposure to different parts of the body may have very different biological consequences. Most of these consequences seem to be restricted to the area irradiated. Also, there is a general agreement that the same dose concentrated on one part of the body is of quite different biological significance than the same dose "diluted" over the whole body. In most instances, the latter has more serious consequences. Only scarce data from animal experiments are available about these problems to date.[24] Thus, at present, it seems hardly possible to compare some of the somatic effects of diagnostic x-ray procedures with the exposures by background radiation.

Exposures of some *specific organs* during diagnostic procedures, however, can be actually measured. The most accurate measurements concern the *skin dose*. At the present time this dose seems to have little significance in diagnostic x-ray. From the genetic point of view, *gonad doses* originating from diagnostic x-ray exposures are very important. These exposures can be measured. There are a number of rather comprehensive measurement series available.[25-31] Table 3 gives a general idea about

TABLE 3.—*Some Mean Gonad Doses (Millirad) Originating from Diagnostic Procedures*[31]

		Denmark	England	Sweden	United States
I. V. pyelogram	M	1,019	486	1,050	2,000
	F	565	1,290	1,820	1,200
Lumbar spine	M	104	129	375	
	F	222	713	680	
Chest film	M	0.36	0.3	1.6	1.2
	F	0.07	0.1	4.6	0.3
Barium enema	M	40	40	255	750
	F	20	20	2,065	1,500

such measurements. As is readily seen, the data of Table 3 show not only considerable differences but are, in some instances, contradictory. This can be explained by (1) poor accuracy in measurements of very small doses, (2) differences in technique of examinations (number of films, voltage, milliampere-seconds, etc.), and (3) differences in technique of protection. This latter point seems to be most important. For instance, the Swedish figure for the mean gonad dose to the male in intravenous pyelography was reduced from 1,050 mrad to 22 mrad by covering the scrotum with lead rubber. Again, according to Hammer-Jacobsen,[23] the male gonad dose in intravenous pyelography can be reduced to 1%-3% of its original value by shielding the scrotum. Evidently, this simple protective technique is not generally practiced as yet. The average gonad dose to the population from diagnostic x-rays can be obtained by using estimates as given in the Table and information concerning the average number and average distribution of different diag-

nostic studies. For the United States, the probable average gonad dose with present technique approaches the same level as natural background radiation. The next radiosensitive tissue of interest would be the hematopoietic organs. The report of the United Nations Scientific Committee on the Effects of Atomic Radiation gives a diagnostic x-ray dose estimate for bone marrow (Table 4), which, again, approaches the level of natural background radiation.

One may knowingly disregard the fact that the biologic significance of exposure to ionizing radiation of different parts of the body is very different. Doing so makes it possible to get a rather rough estimate of the *whole-body integral dose* averaged in a certain population exposed to ionizing radiation by diagnostic x-ray procedures during a single year. An estimate like this was tried and was based on the following data:

1. The number of films and radiation dose per exposure for the various x-ray examinations were calculated from the routine techniques at the University of Pennsylvania Hospital, with use of graphs for calculating integral doses (gram-roentgen), etc., as published by Ritter, Warren, and Pendergrass.[85]

2. The average distribution of diagnostic studies used was that published in *Modern Medicine Surveys*, in August, 1949, and quoted by Ingraham, Terrill, and Moeller.[1]

3. The average integral dose calculated for diagnostic studies was then divided by six (our 160,000,000 people have over 25,000,000 x-ray examinations per year) to give the average integral dose to the population.

	Integral Dose, Gm.-r	Frequency, %	Contribution to Average
Fluoroscopy			
Averaging the doses from 3 min. exams of upper and lower gastrointestinal tract	45,000	14.5	6,600
Photofluororentgenogram			
Chest	8,000	33.6	2,700
Roentgen films (omitting fluoroscopy)—Total, 51.9%			
Chest	3,300	19.3	700
Lumbar spine	208,000	3.9	8,800
Pelvis	115,500	2.2	2,500
Pregnancy	356,000	0.5	1,800
Kidney	47,000	3.5	1,700
Abdomen	7,000	3.4	200
Gastrointestinal series	25,000	9.5	2,400
Gall bladder	14,600	1.3	200
Extremities	10,000	5.1	500
Skull	94,000	3.1	2,900

The sum of this estimate is 31,000 gm.-r per examined person per year. Extending this average over the whole population (instead of 25,000,000 examined persons) of the United States might seem to be pointless at first because a great majority had no x-ray exposure at all during that year. However, such an averaging may be of some significance if the estimate were extended over a period of 30 years. Then it could be assumed that during such a period a large part of the entire population would undergo x-ray studies. Such an averaging would result in an estimate of 5,000 gm.-r per person per year. As previously cited, comparable exposures to background radiation have been estimated to be 7,000 to 10,000 gm.-r per person per year. This estimate of the average whole-body integral dose to the entire population of the United States from diagnostic x-ray studies (5,000 gm.-r per person per year) is in satisfactory agreement with other estimates done with similar methods [20,25,33] (Table 4).

TABLE 4.—*Estimated Average Medical X-Ray Dose to United States Population* [80]

	Genetically Significant Dose, Mrad/Yr.	Whole-Body Integral Dose, Gm.-rad/Yr.	Integral Marrow Dose, Gm.-rad/Yr.
Medical			
(a) Diagnostic	50-135	6,460	135
(b) Therapy	10% of diagnostic?	20% of diagnostic?	20% of diagnostic?
(c) Internal	2-3	Significant dose of 200-400	Significant dose less than 25

With the spread of health-insurance plans, the proportion of the population receiving diagnostic x-ray studies is surely increasing. The estimate of 25,000,000 examinations was made in 1950 by the United States Public Health Service.[1] This increasing proportion undergoing x-ray study could raise the national average radiation

dose to undesirable levels unless greater thought is given to indications for study and decreases are achieved in radiation dose per examination. Generally speaking, we do not feel that there is reason to change the diagnostic usage of x-ray examinations radically. What should be avoided is "generosity" in using x-rays as a diagnostic tool. What we advocate is "stinginess" with x-rays to the extent compatible with the interest of the individual patient.

Concept of Maximum Permissible Exposure.—R. S. Stone,[34] in his Carman Lecture, in 1952, traced the history of our growing awareness of radiation consequences and maximum permissible exposure. As shown in Table 5, the permissible level

TABLE 5.—*The History of Estimates of Maximum Permissible Doses*

Year	Author	Calculated	
		Per Day	Per Year
1902	Rollins	10.0	
1925	Mutscheller, Sievert	0.2	
1926	Solomon	2.0	
1927	Dutch Board	0.04	
1928	Barclay, Cox	0.17	
1928	Kaye	0.12	
1931	Advisory Comm., U. S. A.	0.2	60
1932	Failla	0.1	
1932	Stenstrom	0.16	
1936	Advisory Comm., U. S. A.	0.1	30
1950	International Commission	0.05	15
1956-1957	Advisory Comm., U. S. A.		5

of exposure has been progressively reduced. Some of the reasons for justifiable caution are as follows:

1. There is at present no known antidote to radiation injury once it has been produced. However, prophylactic chemical treatment [35] and bone marrow transplantation can greatly alter the course of radiation damage.

2. Radiation damage is so insidious that it is necessary to carry on an educational program constantly.

3. The outcome of known accidental overexposure has been so serious as to warrant reiterating warnings frequently.

The present maximum permissible exposure for occupational hazards in this country is 5 r, or 350,000 gm.-r per year.[36-40] The British Medical Council report states, "The total dose of extra radiation which may be received by the population as a whole, is not likely to be more than twice the dose which is already being received from natural background; the recommended figure may indeed be appreciably lower than this." The National Bureau of Standards Tentative Handbook 59 states, "The maximum permissible dose to the gonads for the population of U. S. as a whole, from all sources of radiation, including medical and other man-made sources, and background, shall not exceed 14 million rems per million population over the period from conception up to age 30 and one-third that amount in each decade thereafter." [41] This would mean slightly less than 0.5 r per year, or approximately 10% of the present maximum permissible occupational exposure. For simplicity, we have empirically stated that the maximum permissible dose for the population should be three times average background irradiation dose, or 1/10th of the limit on *occupational exposure.*

Occupational hazard, average over population	Less than 105 gm.-r/yr.
Fall-out internal and external dose	Less than 105 gm.-r/yr.
Natural background	10,500 gm.-r/yr.
Medical diagnostic x-ray	5,100 gm.-r/yr.
Total averaged over U. S. population	15,800 gm.-r/yr.

This is about 5% of present maximum permissible occupational exposure level and, therefore, a "safe" level for the population. However, it should be realized that some persons are probably getting biologically significant irradiation from medical diagnostic procedures. The ideal would be no radiation exposure.

In a restricted sense, along with the future outlook for increasing utilization of radiation in medicine and industry and the continuing nuclear explosions, the possibility of further lowering of the permissible exposure level must also be kept in mind.[42] If the permissible level on occupational exposure is reduced to 3 r per year, the

THE HUMAN CONSEQUENCES

Depending upon the cumulative amount of exposure, the frequency of existing diseases and mutations increases

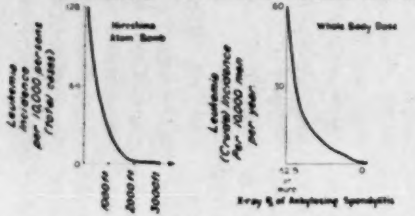
FOR THE INDIVIDUAL

Disease

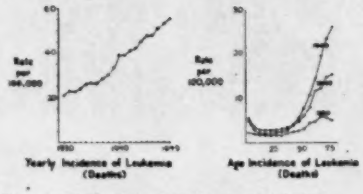
Neoplasia: Cancers of skin, bone, and lung occur after a latent period of 20 or more years in tissue sites previously severely damaged by radiation.

Thyroid Neoplasms have been observed in children after a latent period of about 7 years and after comparatively low radiation doses.

Leukemia incidence is increased with whole body irradiation.


Hiroshima Atom Bomb
Leukemia Incidence per 10,000 persons (Total cases)
100 rads
200 rads
300 rads
Whole Body Dose
Leukemia (Cumulative Incidence per 1,000 male per year)
X-ray Tx of Ankylosing Spondylitis

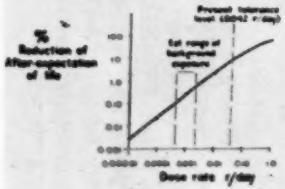
The hazard is cumulative with increased radiation



The possibility that radiation is contributing to this rise must be kept in mind.

Death

Lessening of Life Span: Significant cumulative radiation exposures accelerate most disease processes in a non-specific fashion resulting in shortening of life-span.



Certain estimates for man have been made by extrapolation from data on animals.

AGE AT DEATH

Physicians	65.7
Specialists	63.5
Radiologists	60.5
U.S. population	65.6

CAUSE	Physicians not exposed	Radiologists
NEOPLASIA		
Leukemia	59.0	59.0
Carcinoma of skin	69.0	60.5
Carcinoma other sites	66.7	59.5
DEGENERATIVE DISEASES		
Coronary disease	60.9	58.0
Heart disease (other)	67.1	62.8
Hypertension	70.1	66.1
Cerebral hemorrhage	69.1	60.0
INFECTIOUS DISEASES		
Septicemia	58.9	46.0
Bronchopneumonia	66.7	63.5
Tuberculosis	56.3	51.3
PEPTIC ULCER	63.0	35.5
ALL OTHER STATED CAUSES	66.9	61.8
CAUSES NOT STATED	61.6	61.0

Aplastic Anemia

This occurs as a delayed reaction in both acute therapeutic, and chronic radiation exposure. It must be watched for during any radiation therapy, but it is a rarer complication than leukemia.

Radiation Cataracts

Increased incidence of cataracts has been found following exposure to unusually large doses of neutron or X-ray radiation.

Congenital Malformations

Mother Irradiated:

Developmental defects from irradiation in the first generation are most likely to occur following exposure during the second to the sixth week of gestation, or the fourth to the eighth week following the last menstrual period.

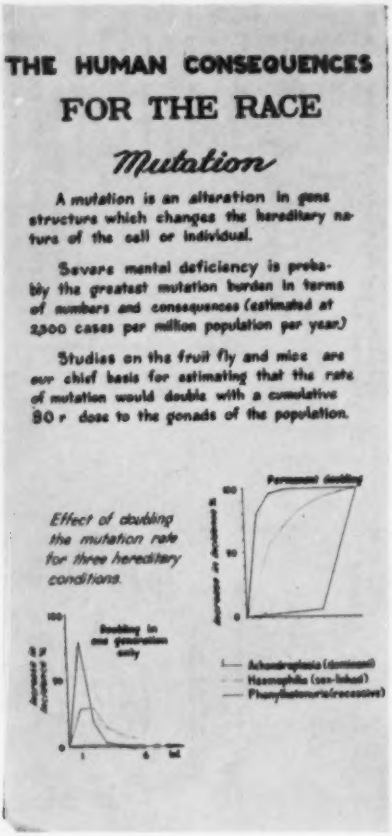
Father Irradiated:

Studies of the offspring of American radiologists show slight rises in the incidence of twinning, foetal death, and congenital malformation. But the results are inconclusive due to possible statistical bias.

Radiation Martyrs

On April 4th, 1936, a stone monument was unveiled in front of the Roentgen Institute at St. George's Hospital, Hamburg, to the memory of radiation martyrs of all nations. In 1938, the names of 197 persons, including doctors, physicists, technicians and nurses, who were known to have lost their lives as a result of X-ray or radium damage, were inscribed on the stone. These were unwitting over-exposures prior to recognition of radiation hazards. Plans are underway to include a further list of names.

Of the thousands of workers in the U.S. AEC facilities during the past 11 years, only 69 were accidentally exposed to excessive amounts of radiation, and of these, only two have died as a consequence.


THE HUMAN CONSEQUENCES
FOR THE RACE
Mutation
A mutation is an alteration in gene structure which changes the hereditary nature of the cell or individual.
Severe mental deficiency is probably the greatest mutation burden in terms of numbers and consequences (estimated at 2300 cases per million population per year)
Studies on the fruit fly and mice are our chief basis for estimating that the rate of mutation would double with a cumulative 80 r dose to the gonads of the population.
Effect of doubling the mutation rate for three hereditary conditions.
Doubling in one generation only
Permanent doubling
Achondroplasia (dominant)
Haemophilia (sex-linked)
Phenylketonuria (recessive)

consequent maximum permissible dose to the population (twice the natural background dose) might be exceeded.

Human Consequences for the Individual Person

Disease

Neoplastic Complications.—These are extensively documented in medical literature as consequences of internal and/or external radiation.[26,43] They might be epitomized as follows. *Cancers of the skin, bone, and lung* have appeared in tissues severely damaged by radiation after latent intervals of 20 or more years. *Cancers of the thyroid* have been reported in children who had received comparatively low dosage of radiation to the neck and chest, with a latent period of about seven years.[44,45] It has been established that *leukemia* incidence increased after acute or chronic irradiation. According to Lewis,[46] for the "average" person in a population, the probability of developing radiation-induced leukemia is estimated to be 2×10^{-6} per rad per year. He speculated that 10%-20% of the spontaneous incidence of leukemia may result from natural-background radiation (in Brooklyn, 1943-1952). The hazard is cumulative and appears to be an effect without "a threshold." The incidence of leukemia as a cause of death for the United States population has increased from about 0.3% in 1930 to about 0.6% at present.[47] There were an estimated 11,500 United States deaths from leukemia in 1956-1957. The increased exposure to diagnostic x-ray may be one factor contributing to the rising incidence of leukemia in the whole population.[48,49]

1. The relationship of the quantity of acute irradiation to increased leukemia incidence has been shown in data from survivors of atomic explosions at Hiroshima[50] and also in data from patients receiving x-ray therapy for ankylosing spondylitis.[51]

2. The relationship to the amount of chronic radiation exposure is shown by the general increased incidence of leukemia among all physicians in the United States and the ninefold to tenfold increased incidence found among United States radiologists.[52] (The 1949 incidence of leukemia at 40 years of age was 3 deaths per 100,000 population).[53] Over the period 1948-1956, leukemia was the cause of more than 7.0% of radiologists' deaths.[54]

3. A possible relationship to single "small" x-ray doses is shown by the report of approximate doubling of the incidence of leukemia and increases in other neoplasms among children who have been irradiated in utero (diagnostic abdominal studies, mainly x-ray pelvimetry of the pregnant mother).[54]

Aplastic Anemia.—This may occur as a delayed reaction in both acute therapeutic and chronic radiation exposure. It must be watched for during any radiation therapy but is a rarer complication than leukemia.

Radiation Cataracts.—Increased incidence of cataracts has been found after unusual exposure to very large doses of neutron or x-ray radiation to the eyes. Careful x-ray therapy technique in proximity to the eyes minimizes this complication.[55]

Congenital Malformation.—Mother Irradiated: The ill effects of irradiation on the fetus are greater than when the whole fetal body is exposed. Developmental defects from irradiation are more likely to occur following exposure during the second to sixth weeks of gestation, or fourth to eighth weeks after the last menstrual period.[56] The evidence from Hiroshima suggests that children are more likely to develop microcephaly when irradiated between the 12th and 18th weeks of intrauterine life. Although occurrence of developmental defects cannot be ruled out (with current diagnostic techniques), the probability of their occurrence is very small. Penetrating therapeutic irradiation to the abdomen during pregnancy may cause abortion or stillbirth as well as a high incidence of developmental anomalies.[57]

Father Irradiated: Studies of the offspring of American radiologists suggested slight rises in the incidence of twinning, fetal death, and congenital malformation, but the results are inconclusive, owing to possible statistical bias.[58]

Death

Shortening of the Life Span.—In the past decade evidence has been accumulated from irradiated mice, dogs, etc., that life span was shortened as a nonspecific consequence of irradiation.[59-61] It has been described as an acceleration of the aging process rather than a consequence of a specific radiation lesion. These studies have demonstrated that this complication probably has a direct dose-size relationship. Most recently, the geneticist W. L. Russell has reported that in mice this shortening of the life span also appears as a shortening of the life span of the first-generation offspring as well. Reliable data are not available for any dose-rate relationship in man.[62] Extrapolations from animal data have been made suggesting that continuous exposure at the rate of 15 r per year (100× background or 3× present maximum permissible exposure [MPE]) might result in a 3% to 5% shortening of life span among those exposed.

Dr. Shields Warren has recently published data concerning differences in life span between radiologists and physicians not exposed to ionizing radiation.[63] The average age of death of the United States population 25 years of age is 65.6 years. That of physicians not exposed to ionizing radiation is 65.7 years. That of radiologists is 60.5 years. These data have been criticized as age-biased by E. B. Lewis.[46] Radiology is a young specialty. The age distribution of radiologists is very different from the age distribution of physicians in general. The radiologist group as a whole is definitely younger than the group of all nonradiologist physicians. Evidently, if and when an average radiologist dies, he would—just on account of difference in age distribution—die younger than would an average physician. According to Seltser and Sartwell,[64] these age differences could explain the rather startling data of Warren. However, Hardin B. Jones,[65] in a reanalysis of some of Warren's data and additional data with use of age-specific death rates, found that although radiologists have the same death-rate risk as the general population at ages under 60, beyond 60 years the death rate of radiologists was about twice as high as expected. These analyses included practically all radiologists who were active in their field in the early 1920's. Self-protecting devices and radiation consciousness were at a low level at that time.[66] The younger group of radiologists still has a shortened life expectancy, but we just do not know how much. An estimate of this effect obtained by extrapolation from animal data is that each roentgen of whole-body dose would shorten life span by 1 to 15 days.[67] Thus, a 30-year exposure at the present maximum permissible dose (MPD) (occupational) of 5 r per annum might result in a decrease of statistical life expectancy of about one year. This shortened life expectancy is about equivalent to that of being 10% overweight.[68] Furthermore, a careful radiologist, even if very busy, should not be exposed nowadays to more than one-fifth of the

present maximum permissible occupational dose.

Radiation Martyrs.—On April 4, 1936, a stone monument was unveiled in front of the Roentgen Institute at St. George's Hospital, Hamburg, to the memory of radiation martyrs of all nations. In 1938, the names of 197 persons, including doctors, physicists, technicians, and nurses, who were known to have lost their lives as a result of x-ray or radium damage, were inscribed on the stone.[69,70] These were unwitting overexposures prior to recognition of radiation hazards. The persons selected for inclusion in the memorial are chosen by the radiological societies of the various countries. At least 105 more names were added to the memorial in 1957 (total 302). The editor of *Strahlentherapie* (Dr. W. Molineus, Hamburg 13, Innocentiastr 22, Germany) is preparing another supplement, with up-to-date biographical notes.

Of the thousands of workers in the United States AEC facilities during the past 12 years, only 77 were accidentally exposed to excessive amounts of radiation, and, of these, only 2 have died as a consequence.[71]

Human Consequences for the Race

Genetic Mutations.—It has not been possible to make a simple noncontroversial statement concerning the implications for man of the genetic effects of radiation.

One view begins with the geneticist Haldane's opinion that even our natural or spontaneous mutation rates are due to natural or background radioactivity. There is general agreement that genetic radiation effects have no threshold. The dose-rate relationship for man has been estimated by extrapolation from data on the fruit fly and mice.[25,26,72-75] Consequently, estimates of the dose causing doubling of the mutation rate vary from 5 to 150 r, with most estimates being 80 r. The manner in which the mutation rate might increase would depend upon the pattern of inheritance and whether the radiation exposure was for a short interval or continuing exposure. At present, it is estimated that 2% of livebirths in the United States have defects which are of simple genetic origin. Many do not impair function of the person. Some, such as mental deficiency, are enormous social burdens. These burdens of deleterious mutants are not easily lost but perpetuate frequently "silently" through many generations. "Statistical extinction of mutant genes is accomplished only through tragedy." [75] However, there are other controllable factors, such as the scrotal temperature, which may also significantly influence the genetic mutation rate.[77]

While very properly being concerned about more mutations due to radiation, we should keep in mind that insulin, antibiotics, and other drugs often save humans whose illnesses are due to hereditary weaknesses which they can transmit to others. No one inhumanely suggests we should not try to save them because of this genetic risk, even though in so doing we are interfering with the natural process for lowering the burden of mutations.

Theoretically, there is no radiation level without increase in frequency of mutation. The permissible limits appear to have an effect comparable to, and probably less than, that of unavoidable natural exposure.

The Search for Solutions

Education.—Occasional and part-time x-ray users have the same responsibility for proper technique and safety precautions in using x-rays as any physician utilizing a potentially toxic agent.[78] This problem is being recognized by those attempting to evaluate radiation hazards. Zavon, in a recent editorial in *The Journal of the American Medical Association*, cited fluoroscopy in particular as being often done under conditions recognized as unsafe, and he stressed, "The physician who uses x-rays or radium should make sure that the newer knowledge of radiology is being applied in his practice." [79]

Some observers feel that more stress should be placed on radiological techniques

in the general internship and residency training programs. Chamberlain has stated, "that physicians, other than radiologists, who need to use radiation in certain fields, can, and should, receive training in the special problems of radiation protection."[80] The findings of Sonnerblick[81] tend to bear out a difference in usage of radiation between the radiologist and nonradiologist. He found that for similar-sized patients under a fluoroscope a radiologist might be using 1 ma. and producing a dose rate of 2 r per minute at the panel; the internist, 2 ma. with a dose rate of 20.3 r per minute, and the pediatrician, 5 ma. with a dose rate of 43.8 r per minute. The accepted level of radiation at the time of his report was 20 r per minute and has since been decreased to 10 r per minute.

It is felt that basic training in simple fluoroscopy and protection techniques requires at least six weeks' full-time training under a radiologist's supervision.

Innovations.—The radiation dose to gain diagnostic information is being sharply reduced by innovations. The Graph in the present paper is from data of the Nuffield Institute for Medical Research at Oxford.[82] The innovations resulting in these improvements for a 5-in.-diameter-area abdominal film are as follows: Barclay (1939), on the advice of Professor Mayneord, reduced the skin dose from 1.4 to 0.8 r by introducing a 2 mm. of Al filter and by increasing the focus-film distance. McLaren, Ardran, and Sutcliffe (1950) further reduced the dose to 0.25 r by further increasing the focus-film distance by the addition of another 1 mm. Al filtration and by the substitution of faster film for standard film; this reduced the depth dose at least 50%. Ardran (1952) reduced the skin dose to 0.13 r and the depth another 50% by using about 90 kvp and fast screens. Ardran and Wyatt (1953) found that by using an image intensifier both the depth dose and the skin dose might be reduced by a factor of 10.

Improved image intensifiers eventually will permit reducing the patient-radiation dose probably by a factor of 10 and should not be squandered in doing away with "dark adaptation." Further equipment improvements and wider usage in routine examinations should bring marked reduction in patient-radiation dose.

Therapeutic irradiation for benign lesions should be avoided as much as possible, especially if other methods are available. For malignant lesions, therapeutic irradiation apparently is not influenced by consideration of radiation hazards.[83] However, it would be advantageous to give more attention to the exact beam-directed methods of British radiologists. They are not only more effective but also require less integral or volume dose.[84]

Selective tissue radiation can be achieved with some radioactive isotopes and colloids, decreasing the accompanying whole-body dose.

Good Technique.—In evaluating the hazards of x-ray and nuclear radiation the objects of radiation protection must be kept in mind:

1. The doctor must be protected.
2. The technician must be protected.
3. The patient must be protected.
4. The neighbors must be protected.

Techniques in handling radiation should be established with this consideration, and the following points have been proposed:[85-88]

1. In radiation therapy, neither the radiologist nor any member of his department should be in the room with the patient undergoing treatment.
2. In fluoroscopy, great care must be exercised to be sure that there is no leakage of radiation around the screen. The screen itself must be covered with lead glass of sufficient thickness to stop all radiation, at least 1.5 mm. lead equivalent, and be mounted in a protective frame.
3. In addition to this protection from the direct beam, it is essential to provide shielding against radiation scattered from the patient and from other objects in the room. A lead-rubber apron or protected chair, lead equivalent at least 0.5 mm., should cover the body from the chest to the floor.
4. Persons observing the fluoroscopic room, who are not protected by the screen, may require more complete protective clothing than the radiologist himself.
5. Almost full gonad protection of the male patient, in radiography and especially in abdominal fluoroscopy and therapy, is feasible and should be

THE SEARCH
Good Technique
In fluoroscopy, great care must be exercised to be sure that there is no leakage of radiation around the screen. The screen itself must be covered with lead glass of sufficient thickness to stop all radiation, at least 1.5 MM. lead equivalent, and be mounted in a protective frame.
In addition to this protection from the direct beam, it is essential to provide shielding against scattered radiation from the patient and from other objects in the room. A lead rubber apron and protected chair lead equivalent at least 0.5 MM. should cover the body from the chest to the knees.
Doctors observing the fluoroscopic room, who are not protected by the screen, may require more complete protective clothing than the radiologist himself.
All manipulations should be carried out as rapidly as possible, consistent with accuracy. The smallest acceptable fields should be used. Great care should be exercised to use the hands in the X-ray beam as little as possible, and never without lead rubber gloves. Target-skin distances should never be less than 30 CM. nor filtration less than 2.0 MM. AL.
Education
Occasional and part-time X-ray users have the same responsibility for proper technique in using X-ray as any physician utilizing a potentially toxic agent.
Basic training in radiologic techniques and protection requires at least 6 weeks' full-time training under radiologist supervision.
Innovations
The radiation dose to gain diagnostic information is being sharply reduced by innovations.
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carried through as a routine.[50] Development of useful ways and devices is going on, including protection of female gonads, which is now feasible in many cases. No generally accepted procedure is in practice now, but committees of the American College of Radiologists and the American Medical Association may soon describe recommended practices.

6. All manipulations should be carried out as rapidly as possible consistent with accuracy. It is important for beginners in fluoroscopy, and especially for the fluoroscopist who is not a radiologist, to use the smallest possible opening of the shutter and make this a life time habit. Experienced radiologists do that anyhow, but even they may use excessively large openings inadvertently when fluoroscoping with the present-day image intensifier. The visible field of this is very small, and it may happen that a large shutter opening is used without the radiologist knowing about it. Installation of an adjustable "danger signal" was suggested by one of us some time ago to some United States x-ray companies.† The acoustical (or optical) signal would be given whenever the opening is larger

† Such an arrangement was devised, constructed, and patented (D. R. P. 568 694) in 1930 by one of us. This device worked in a mechanical way, automatically decreasing the size of the opening of the shutter as the lever of the shutter was released to a desirable opening. It was manufactured for about four years. Then the manufacturer (Siemens, Reinigert, Veifa, of Erlangen, Germany) discontinued it because there was not enough interest for it at that time. Radiologists were not as x-ray-protection conscious at that time as they are nowadays.

FOR SOLUTIONS

Health Records

It has been proposed that records should be kept of an individual's medical exposure to radiation. If this record were kept by the peripatetic patient, it might be part of a general health diary containing blood type, transfusion history, immunization, allergy, and infectious disease history. It has been stated that such radiation records would be inaccurate, cost excessively, cause radiation phobia and would be frequently lost. Other proposals include use of industrial medical departments, hospital radiology departments, and physicians' offices as depositories for such information. The need and usefulness of such records of diagnostic roentgenologic studies are under dispute. The patient's need for such records of therapeutic radiation is more generally recognized.

Legislation

Several states and a few municipalities have regulations in regard to some radiation hazards. If such legislation is desirable, or even inevitable, then it should make use of the experience of radiologists and health physicists and Handbooks of the National Bureau of Standards (*Recommendations of the National and International Committees on Radiation Protection*)

Revision of Medical Usage

Avoid:

a. Therapeutic radiation to benign lesions:
e.g. Epilation, acne, bursitis

b. Prophylactic diagnostic X-ray procedures:
e.g. X-ray pelvimetry without clinical suspicion of abnormality
e.g. Short interval re-evaluation of duodenal ulcers or following removal of benign polyps

c. Abdominal radiation to women in childbearing age beyond 2 weeks after last menses.

Justified Procedures Should Be Done Without Hesitation:

a. Solving existing diagnostic problems

b. Repeat evaluation in cases of known malignancy

c. Routine chest films at yearly intervals

Age Factors:

a. Up to 30 years of age, strictest precautions should be applied to use of X-ray procedures.

b. From 30 to 50 years, precautions can be relaxed as potential childbearing decreases.

c. After 50 years of age, even benign lesions might be treated with X-ray, if its superior therapeutic efficacy is recognized

than desirable. This would not impede fluoroscopy with large openings (sometimes necessary for a short time). We understand that industry is just about to put such a device on the market.

7. Great care should be exercised to use the hands in the x-ray beam as little as possible and never without lead-rubber gloves. Target-skin distances for radiography should never be less than 75 cm. For fluoroscopy, most present-day machines are set for target-skin distances of 45 cm. It would be advisable to have target-skin distances increased to not less than 60 cm. for fluoroscopy.[90] Filtration should not be less than 2.0 mm. Al, and 3.0 mm. is preferred.

Health Records.—Radiation has been shown to have a cumulative effect on animals. The total exposure, as well as the amount of each exposure, has been shown to be important in assessing chronic radiation effects. On that basis, the suggestion has been made for the adoption of a nationally standardized personal radiation-diary system.[91] However, there are still insufficient data covering the range of exposures encountered in occupational hazards and chronic illness to prove the proportionality of chronic low-dose irradiation to the incidence of undesirable radiation effects.[24,92-94]

One proposed use of a universal radiation-diary system would be as a means of estimating the gonadal radiation dose to the population. However, a universal system

seems unfeasible because of inaccuracies in measurements due to widespread lack of instruments and trained personnel. Further prejudice arises from the excessive cost in time and money to medical personnel and possible interference with proper medical care owing to radiation phobia. Much greater accuracy with smaller expenditures could be obtained with proper sampling procedures, utilizing persons skilled in radiation measurements. A further advantage of such sampling studies would be the adaptability to covering questions of allied interest (distribution of dose delivered by various types of radiation practitioners, including doses to other parts of the body, to serve as an aid in estimating systemic damage, e. g., leukemia, shortening of life span, etc.)

Another proposed use of a radiation diary would be as an estimate of the somatic radiation dose to the individual person (especially those with occupational exposures). Again, the factor of error in dose estimation must be raised. Some persons negate this problem by stating it would be sufficient to list the type of examination and the date. It is possible that medicolegal aspects might result in some fudging of the recorded information. Such records would probably be frequently lost. A most important consequence might be that such a radiation diary would result in a patient refusing or a physician withholding a further necessary diagnostic study. There are still insufficient data to weigh clearly the radiation risk from diagnostic studies, with equivocal medical justification, against the disease risk of unsuspected lesions.

The debates over a radiation diary cover mainly the practicality, the cost, whether the data would be sufficiently accurate to have value, or what its value would be when all x-ray exposures are medically justified. Secondary debates are over the type of data to be recorded—ranging from one extreme covering areas exposed, milliamperage, kilovoltage, filtration, distance, dosage rate, and total volume dose in gram-rad to a simple dated list of roentgen examinations.

If accurate data permitting some sort of biological integration could be recorded practically, there is general agreement on the advantages which would accrue. It would stimulate better planning and stress the importance of unnecessary radiation exposure in treatment of current or future problems. It would instill more radiation consciousness in the average practitioner using radiation equipment and, thereby, tend to increase the use of protective devices and timers and result in better control and supervision of fluoroscopy. One should not forget that in 1950 less than 5% of medical x-ray units were used under supervision of radiologists, i. e., of people who are most conscious of necessary radiation protection. Individual radiation records would call attention to the fact that the individual person has a "reserve" of radiation tolerance, which, when drawn, cannot be replaced. The hitherto careless recorder would be compelled to improve his methods. The system would also have legal and insurance value because it would help to distinguish between negligence and necessary heavy irradiation. (Note: The latest recommendations of the National Committee on Radiation Protection include the statement, "It is the responsibility of the attending physician to evaluate medical radiation exposure in relation to the health of the individual.")

If radiation records were kept by the peripatetic patient, it might be part of a general health diary, containing blood type, transfusion history, immunization, and allergy and infectious-disease history, as well as medication dosage, such as for insulin and cortisone. The person would have greater tendency to preserve the record and keep it current if it contained this frequently needed information. A more sophisticated attitude toward potential radiation hazards might result from comparison of these with the potential hazard of other diagnostic and therapeutic procedures, as well as those hazards commonly encountered in daily life. Other radiation-record proposals include use of industrial medical departments, hospital radiology departments, and physicians' of-

fices as depositories of such information. Although the need and usefulness of records of diagnostic roentgenologic studies are under dispute, the patient's need for records of therapeutic radiation exposures is more generally recognized.

Whether or not personal radiation diaries are established, it would be wise for the individual radiation practitioner to have measurements and calculations recorded of the average radiation dose delivered by his equipment and technique for his routine diagnostic x-ray studies. Periodic repetition of these measurements and calculations should also be carried out.

Legislation.—In viewing the present hazards of radiation, it is evident that extensive control and safeguards will be necessary with the continued increased use of x-radiation. At present, there is a fairly general attitude that the precautionary safety measures should be initiated by the various users of radiation without legislative intervention until acceptable and uniform regulations can be adopted.

The National Committee on Radiation Protection has discussed this problem extensively.[95] It concluded that there are three possible solutions:

1. The least restrictive solution, yet one that might prove most effective in the long run, would be one following present broad policies augmented by a widespread program of education.

2. The second possible solution would be one in which all sources of radiation are registered. This would allow evaluations of all uses and, if indicated, inspection with recommendations. In general, the user would watch his own practices carefully, knowing they would be open to inspection.

3. The third solution would be one calling for inspection and licensing of all radiation sources. It would be costly and difficult to administer.

The National Committee on Radiation Protection, as well as the International Committee on Radiation Protection, feels this last solution is impractical at the present time. They have directed their efforts toward the development of basic protection data and information, with recommendation of codes of safe practice when necessary. However, with the rapid growth of the protection problem in recent years, this may become inadequate.

Objections to legislative actions at present are primarily concerned with inability to enforce them. One of the strongest arguments against licensing is the magnitude of the task. To have a program which is not properly staffed and supervised would give a false sense of security to radiation users. With the existence of the regulatory body, the user would continue to have responsibility, as he now has; however, he would lean more and more upon the control group to assure him that his precautions are adequate. This endeavor would be so enormous that the nation as a whole lacks the radiation experts necessary to implement it.

The cost of such a program would become a public problem. It could be financed by one of three ways: (1) by fees paid by the user, (2) by appropriation of funds, (3) by a combination of fees and appropriated funds. If the first method were used, it would, in some instances, make the use of radiation prohibitive. If the second method were used, it would place a burden on the taxpayer to which he would have a legitimate objection. The third method would pose several legislative problems; however, it would probably be the most practical.

Several countries have already tackled legalistic problems of radiation protection.[96] However, in all except those with state health-insurance plans, most of the responsibility of enforcing radiation protection has been placed on the users, supplemented by a vigorous educational program.

During the first session of the 85th Congress, bills were introduced in both the United States Senate and the House of Representatives (S1228 and H. R. 4820), which would establish a National Radiation Health Institute with power to initiate control programs and engage in educational and research activities.[94] The bill would also establish an Office of Radiation Health Control empowered to carry out the recommendations of the National Academy of Sciences relative to the radiation diary mentioned before. There has been criticism

of this move on the basis of the factors discussed before, and it is felt that there is a need for pilot programs instituting the above systems in order to gain sufficient knowledge and experience to make feasible a program of the magnitude of one enacted by law.[78,97]

Revision of Medical Usage.—With the increased knowledge which is being gained by widespread and extensive studies on the effects of irradiation, it is being realized that doses of radiation previously considered harmless are in fact creating a potential danger to the population.

Responsible organizations[98] have been reluctant to include the medical usage of radiation in their recommendations; however, a point has been reached where some groups[99] feel that medical irradiation, especially that used for diagnostic purposes, will require reevaluation. Dr. Shields Warren, representing the United Nations Committee on Effects of Atomic Radiation, in a recent address (as quoted by the press) pointed out that Americans are being exposed to 43 times as much harmful radiation from medical and dental x-rays (i. e., about 43% background) as from atom tests (i. e., about 1% background) and urged a vigorous movement to cut the exposure to x-rays to the lowest limit consistent with medical necessity.

The National Academy of Sciences has made recommendations that man-made radiation exposure to the individual person be limited to 50 r gonadal dose during the first 30 years of life, with no more than 50 r during the period from 30 to 40 years of age. The recommendation was also made that the average man-made dose to the population should not exceed 0.1 of this amount. The average man-made dose per person would be *limited* to 10 r during the major portion of his reproductive life.

Some committees[100,101] feel that there has been a lag in concern on the part of the medical profession about this problem, and this may bring about legislative action if not improved. Recent medical literature has shown physicians to be examining with care the problems of medical radiation exposures. Such studies, along with further information on the consequences of chronic low-dose irradiation, will ultimately provide solutions. Certainly, most unnecessary reexaminations could be eliminated by examining previous roentgenograms from other examiners and by routinely including in the patient interview questions concerning previous x-ray studies and treatment. Determining the necessity for added x-ray studies is the responsibility of the physician requesting x-ray studies, not of the examining radiologist. Radiologists, as consultants, have the responsibility to assist in clarifying the indications for x-ray studies in general. It behooves us, therefore, to continue reevaluating the indications for x-ray examination and treatment in light of new facts. In such a reevaluation, the possible damage caused by a certain radiologic procedure must be weighed against possible damage caused by *omission* of the same. The following statements represent our (J. G. B.) radiologist's personal opinion in a field in which there is no general agreement. However, there are certain facts which would allow the following recommendations as to which procedures, now practiced, could be revised.[79,102-106]

1. *Procedures to be avoided as a rule:* Radiation treatment of most of the benign lesions (enlarged thymus; sterilization of ovaries for benign bleeding; arthritis; self-limited inflammatory lesions; alleviation of pain in nonmalignant conditions, e. g., bursitis; cosmetic problems, e. g., acne; irradiation of stomach for hypersecretion in young persons; cosmetic epilation and destructive irradiation of benign skin conditions, such as warts or birth marks).

2. *Cases in which usage of x-ray procedures should be avoided as a preventive measure:* Repeated routine examination of the abdomen for pregnancy *without* clinical suspicion that something might be abnormal and of clinical interest; routine pelvimetry *without* clinical suspicion of abnormality; *short interval serial check-ups* after surgery of polyps, or of known stomach or duodenal ulcer; routine examination of stomach or colon *without* clinical suspicion of disease; any fluoroscopic examination as a routine *without* clinical suspicion of disease.

3. *Justified procedures:* Any generally accepted procedure to solve *existing* diagnostic problems; any diagnostic or therapeutic procedure, including

regularly repeated check-ups, in cases of known malignancy; preventive routine chest examinations (radiographic, preferably full-size films), however, not more often than once in six months.

In any dubious case, an important factor is the *age* of the patient. Any radiation increases the probability of damage, and this is the more so as the years go by. Other things being equal, the younger patient will be subject to the same hazard longer than an older one. Therefore, increasing age may make radiologic indications more liberal.

It has been suggested that certain x-ray examinations in women of child-bearing age in whom full protection of the gonads is not possible should be restricted to periods in which there is little possibility of unrecognized pregnancy. This would, in that age group, reduce the time available to radiologic procedures by nearly 50%. The justification of such a request is, at the present time, based on theoretical considerations rather than on observational or experimental facts. Nevertheless, such an idea is definitely worthy of consideration.

Summary

The citizen physician should be prepared to help maintain proper perspective in community discussions on radiation hazards. A new responsibility of physicians to evaluate medical radiation-exposure effects on the individual patient's health is pointed out.

There is general agreement that there are deleterious effects from high levels of radiation exposure. There are insufficient data to fix the extent of deleterious effects from the relatively low levels of radiation received in medical studies. Individual conclusions vary from one extreme, that the numbers of radiation-induced leukemia cases are large, to the other extreme, where the relative magnitude of this radiation hazard is insignificant when compared to usual everyday hazards.

"Putting all of these diversions aside I think our course today is relatively clear.

"We must minimize our exposure to radiation. We must maximize the benefits it offers to our health and our material well-being.

"These two aims are mutually contradictory as far as we know today. Radiation protection is not only a matter for science. It is a problem of philosophy, and morality, and the utmost wisdom." [107]

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Pernicious Anemia, 1822-1929

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More than a century elapsed between the first description of a case of pernicious anemia, by Combe, of Edinburgh, in 1822, and the investigations of Castle and his colleagues, which mark the beginning of our present understanding of the disease. This paper gives an account of the work carried out during that period in defining and investigating the condition.

Clinical Observations

A paper [1] entitled "History of a Case of Anaemia," read by Combe, on May 1, 1822, contains the first authentic description of a case of pernicious anemia. The patient was a corn merchant's servant, aged 47 years, who had always enjoyed perfect health. When Combe was first consulted he was immediately struck by the man's peculiar appearance. "His face, lips and the whole extent of the surface, were of a deadly pale colour . . . his motions and speech were languid; he complained much of weakness . . . the inner part of the lips and fauces were nearly as colourless as the surface." He complained also of diarrhea and sickness. On examining the patient, "He has no pain referable to any part, and a minute examination could not detect any structural derangement of any organ." In less than a year the patient died, having first become wasted and edematous. In his conclusion Combe remarks, "It is probably owing to some disorder of the digestive and assimilative organs, that its characteristic symptom (anaemia) has its origin, and to the correction of this derangement, we must look for a removal of the disease."

It should be noted that Young [36] had previously classified anemia under the general heading of dyspepsia, though he makes no specific comments on the relationship.

Addison's account of the disease,[2] in 1855, describes: "A very remarkable form of general anaemia, occurring without any discoverable cause whatever—cases in which there had been no previous loss of blood no exhausting diarrhoea, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease. Accordingly, [he writes] I applied to it the term idiopathic. . . . It occurs in both sexes . . . beyond the middle period of life, and, so far as I at present know chiefly in persons of somewhat large and bulky frame." At the end of the clinical description which follows Addison states, "I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences." The absence of any obvious etiological factor became an important diagnostic feature, particularly among English physicians.

The term "progressive pernicious anemia" was introduced by Biermer [3] 17 years after

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Addison's monograph. He used it to describe a group of anemias having similar clinical features to Addison's anemia but in which a cause for the disease was often found. The commonest factors were intestinal disorders, infestation with fish tapeworms, and pregnancy. He mentions cases in which no cause for the anemia could be found, but by including such a diversity of diseases under this heading he obscured Addison's original concept of an idiopathic anemia. The term "pernicious anemia" was often used loosely to indicate a severe degree of anemia regardless of the cause.

In an important lecture on idiopathic anemia, in 1881, Coupland [4] proposed a classification of anemias which is surprisingly close to the modern view and which accommodates both Addison's and Biermer's types of pernicious anemia.

- Anemia
  - Symptomatic
    - Simple
    - Pernicious (Biermer)
  - Idiopathic
    - Simple
    - Pernicious (Addison)

He gives as the three main causes of symptomatic pernicious anemia (1) bad living and food, (2) pregnancy, (3) digestive and intestinal disorders. There is also a short note in this paper of a case found at postmortem examination to have a gastric polyp —the earliest mention of this finding.

During the following years many new facets of the clinical picture of pernicious anemia were discovered. In 1884, Lichtenstern [5] described two patients who also suffered from tabes dorsalis, but there is little doubt that these were in fact cases of subacute combined degeneration of the spinal cord. Putnam [6] later reported four cases and thought that the spinal lesions were probably due to the same hypothetical toxin that was responsible for the anemia. He pointed out that these lesions did not arise in chlorosis and were thus probably not due to the anemia itself. Russell et al.[7] recorded nine cases, in none of which was there any evidence of pernicious anemia. They also concluded that the disease had a toxic origin.

Klein, in 1891, described three siblings,[8] all of whom suffered from pernicious anemia in adult life. This is the first mention of the familial incidence of the disease, which was later noted by Gulland [9] and Weinberg,[10] who also showed that some of the relatives of patients with the classical disease have gastric achlorhydria—a phenomenon he called pernicious anemia without anemia.

Gulland's paper of 1907, entitled "Anomalous Cases of Pernicious Anaemia," makes our knowledge of the clinical condition complete. He refers to cases presenting with amaurosis and peripheral neuritis, and among the cerebral manifestations he mentions the occurrence of depression and delusional states with hallucinations.

Hematological Investigations

The first comprehensive account of pernicious anemia is Eichhorst's "Die progressive perniciöse Anämie"[11] which appeared in 1878. It includes a review of the historical, clinical, hematological, and pathological aspects of the disease. There is a description of the characteristic peripheral blood picture, with a low red cell count and the presence of both abnormally large and small cells. The important observation that the red cells although reduced in number contain a normal amount of hemoglobin was first recorded by Hayem.[12] Quincke [13] showed that the liver contained an excessive amount of hemosiderin, and he also noted the presence of poikilocytosis in the peripheral blood.

Pepper [14] is usually credited with the first description of the bone marrow changes in pernicious anemia, but the diagnosis in the case he described is by no means certain. A more convincing account was given by Cohnheim,[15] in 1876. He described the postmortem findings in a man aged 35 years. The bone marrow appeared redder than normal and extended to parts of the skeleton not usually containing red marrow. Microscopic examination showed not only the characteristic anisocytosis of the red

cells but also the presence of occasional cells with large vesicular nuclei. While realizing the inconclusive nature of evidence drawn from one patient only, Cohnheim considered that the disease was primarily a disorder of hemopoiesis.

The work of Erlich and Lazarus [16] confirmed that the bone marrow was abnormal. Their book "Die Anämie," published in 1898, includes a description of the megaloblast, an abnormal form of nucleated red cell, which is found only in cases of pernicious anemia. Their concept of the disorder corresponds to the clinical definition of Biermer, and so all cases in which megaloblasts are found are automatically classified as pernicious anemia. It is not surprising that in view of the marked abnormality found in the marrow this was thought to be the basic abnormality from which other symptoms arose.

Gastrointestinal Tract

In the year before Combe's paper introducing pernicious anemia as a new disease, Prout [17] demonstrated the presence of free hydrochloric acid in the gastric juice and showed that it constituted by far the largest part of the gastric acid. Although this was rapidly confirmed,[18] the observation achieved little clinical importance until after the introduction of the stomach tube for purposes of routine gastric analysis by Leube,[19] in 1876. His procedure involved the feeding of a test meal, composed of beef stew, potatoes, and bread, followed by aspiration and examination of the stomach contents seven hours later. Modifications of this technique included the "one-hour test meal," introduced by Ewald and Boas,[20] and much later the fractional gastric analysis of Rehfuss,[21] who described his modified stomach tube in 1914.

Austin Flint [22] appears to have been the first to implicate disease of the stomach as the causative factor in pernicious anemia. He suspected," . . . that in these cases there exists degenerative disease of the glandular tubuli of the stomach." In 1877, Fenwick [23] described four cases of pernicious anemia which were studied both during life and post-mortem. In all cases there was a striking atrophy of the gastric mucosa, which led him to believe that this was the cause of the disease. He wrote, "As it is the especial function of the stomach to dissolve the albuminous portions of the food so a gradual failure in its powers necessitates a diminution in the volume of the blood."

The tubular glands of the gastric mucosa were identified as the site of acid production by Langley,[24] in 1881, and he named them "oxyntic glands." The detailed morphology of the actual parietal cells, including the intracellular canaliculi, was described by Zimmermann,[25] in 1898. The association of pernicious anemia with achlorhydria was first observed by Cahn and von Mering [26] and Martius,[27] who recorded altogether three cases, but the association was not universally recognized until the later confirmation provided by larger series of patients.[10,28] The introduction of histamine as a stimulus to gastric acid secretion [29] only served to emphasize the almost invariable presence of achlorhydria in cases of pernicious anemia.

The first serious attempt to understand the role of the gastrointestinal tract in the etiology of pernicious anemia is that of William Hunter.[30] In his book "Pernicious Anaemia," published in 1901, there are the results of much clinical and experimental observation. He considers the disease to be due to the hemolytic process caused by a poison "of some special bacterial nature produced within the gastrointestinal tract" and resulting in anemia and severe hemosiderosis, especially in the liver. He stresses the frequency of dental caries, stomatitis, and glossitis and thinks it probable that the infection spreads down into the intestines. Remissions are due either to a lessening of infection or to increased resistance by the patient. It is interesting that Hunter makes no mention of abnormal hemopoiesis and states, "So far as the bone marrow is concerned, I have not found the changes suffi-

ciently constant or sufficiently distinctive to throw any light on the nature of the disease."

This view remained prominent during the first two decades of the present century, although not without some criticism.[9] The final flowering of the intestinal infection theory is seen in Hurst's account,[31] which appeared in 1924. On scanty evidence, later refuted by Castle,[32] the disease is thought to be due to the presence of a hemolytic Streptococcus in the intestines, with the subsequent absorption of its toxins. The failure of the antiseptic barrier provided by the gastric acid is instrumental in bringing about this state of affairs. In an attempt to reduce streptococcal infection Hurst recommends treatment of the sinuses, tonsils, and teeth. "In most cases," he says, "every tooth will have to be extracted." Hydrochloric acid is given orally to increase the antiseptic properties of the stomach and charcoal to absorb the toxins. An autogenous vaccine prepared from the patient's duodenal flora is also given to increase resistance.

In 1926, the work of Minot and Murphy[33] revolutionized the treatment of pernicious anemia. Forty-five patients suffering from the disease were treated with a high-protein, low-fat, and low-carbohydrate diet, which included a minimum daily allowance of 120 gm. of liver and 120 gm. of beef or mutton. They all showed a remarkable clinical improvement. Cessation of diarrhea was followed by a rise in the reticulocyte count after 5-14 days and then a gradual hematological recovery. All the patients remained well on this diet, and at the time of publication 12 patients had been under treatment for over a year. This was the first treatment for pernicious anemia which produced such a universal and well-maintained improvement.

Three years later, Castle's first "Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia" appeared.[32] In it he gives a lucid review of past knowledge of the disease and deduces the foundation for his new theory. He notes that gastric achlorhydria is the only symptom of pernicious anemia not cured by treatment with liver but that acidity may return during spontaneous remissions. Achylia is thus implicated as a prime factor in causing the disease. The response to liver treatment indicates that pernicious anemia is a deficiency disease, but as many people do not eat liver the important factor must be found in many foods. Castle proceeds to show how a remission may be induced by the oral administration of gastric juice obtained from a normal person in the process of digesting beef muscle.

Further investigations[34,35] showed that a factor present in beef reacted with normal gastric juice in vitro to produce a substance capable of causing a remission in cases of pernicious anemia. The gastric factor corresponded to none of the known constituents of the gastric juice and was called the "intrinsic factor." It was absent from the stomach in pernicious anemia, and this deficiency was thought to be the cause of the disease. More recent work has served only to verify and amplify the results of these classic experiments.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

Six Wings: Men of Science in the Renaissance. By George Sarton. Price, $6.75. Pp. 318, with illustrations. Indiana University Press, Bloomington, Ind., 1957.

The late George Sarton, one of the most distinguished historians of science of our time, was founder and editor of *Isis*, and of *Osiris*. The "Six Wings" consists of the substance of the Patten lectures he delivered at Indiana University in 1954-1955. Professor Sarton died in 1956 and thus did not read the proofs or make an index, but someone did them well. A useful running head to the notes sections indicates the pages as well as the usual chapter headings, and so one does not have to go back and forth so much. The typography and printing do justice to the elegance of the lectures, and the beautiful illustrations, mostly portraits of the subjects of the book, are a rich example of the care and love which went into the book. Sarton spared no pains to get the best and most accurate portraits available. Part of the motivation for this searching analysis of science and the Renaissance hovers around the unhappy fact that while artists and people interested in art are anxious to learn all they can about the lives and ideas of other artists as creators of beauty, but most scientists care little for the history of science. Part of the training in art is copying masterpieces created by other artists. Sarton wants to know, "Is it less natural for scientists to want to know all that he can about the lives as well as the works of his predecessors?" He answers his own question by pointing out that some scientists are technicians who want merely to master facts, theories, and tricks of the trade and have no curiosity or time left for anything else. Even for a physician not interested in history, this book on men of science and the Renaissance will be a stimulus and should awaken a genuine interest in the men who have made science. Sarton apologizes for not being able to make a book of this kind all-inclusive, but he has selected wisely and in his imaginative and scholarly analysis has opened up for us the wings upon which the men of science in the Renaissance soared. The first wing deals with exploration and education. The great discoveries of the period between 1450 and 1600 brought most of the globe under observation and produced an excitement and wonder which spread like bubbling yeast through the times. To a remarkable degree, education was stimulated by men of genius and their work was organized and kept alive in institutions which enabled scholarship to thrive. The Latin language kept open the channels of communication for all learned men. But vernaculars, the peoples' tongues, were on the rise, with all the infinite possibilities of creating genuine styles possible only in a living language. Out of this period arose the languages of English, German, French, and Italian, just to mention some of those most important in the propagation of knowledge and the advancement of learning.

The second wing of the Renaissance flight of science was mathematics and astronomy. Sarton emphasizes the long painstaking struggles to deal with mathematical concepts when there was no common symbolic language even for algebra. Nevertheless, mathematics grew and had great influence in painting, where the theory and employment of perspective were being developed. This required knowledge of trigonometry. Since the symbols used in mathematics were fragmentary, arbitrary, and unstandardized to the point of chaos, mathematics was kept back by the need to use literary rather than symbolic terms. Each of the notations, such as $+$, $-$, $=$, came in separately. Each took a long time to get established. With wider diffusion of knowledge, it was not rare for new ideas to come in independently and simultaneously. Algebra, one of the earliest fields of mathematics to develop in antiquity, received a fresh impetus from Cardano, a man of many paradoxes, among many who made great contributions.

The main astronomical event of the Renaissance was the publication of Copernicus' "Revolution of the Celestial Spheres," in 1543, the same year which saw the publication of Vesalius' "Fabrica." With Copernicus, Kepler, and Brahe, astronomy began its flight away from

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

astrology. At length it became possible to revise the calendar, a considerable feat amidst religious differences and the multitude of small and changing political units of time. Man's place in nature and his image of himself were beginning their long shift from geocentric to egocentric and finally accentric.

The third wing is constituted by physics, chemistry, and technology. Mechanical sciences developed on the principles of solid geometry as well as the empirical knowledge of hydraulics. Ballistics arose with the use of gunpowder. Optics advanced with astronomy but was not too proud to help in the development of spectacles. Navigation required an understanding of astronomy. Knowledge of magnetics facilitated the development of the compass. Exploration encouraged the emergence of cartography. Progress in techniques, skill in performance, and scientific knowledge were all mutually supporting. The early Italian scientific academies were born. They were substitutes for a journal literature of science supplying a forum for the complex interweaving of ideas which helped the rapid progress of knowledge during the Renaissance period. Chemistry, which had not escaped the shackles of alchemy, was beginning to stand on its own feet, though Porta's "Natural Magick" indicates what a long way it still had to go. Of all the technological advances, the development of printing with movable type, which permitted a hundred different persons in a hundred different places to read the same thing, which fixed quantities and data so that errors could be detected and changed in subsequent editions, though it bore the seeds of the ultimate superstandardization of mass media, made possible not only the birth of science but the organization and codification of knowledge.

The fourth wing, natural history, had its earliest beginnings in ancient botany. When printing became available, with widespread use of woodcuts it was possible for a publisher to have a large collection of plates which he could use for illustrating a number of different books. Early botanic gardens began to develop, and large collections of dried plants were assembled. Some order was forming in the pharmacopoeia, hitherto a mark of the power of authority blended with superstition. Early but rather tentative movements in the direction of physiology had appeared. Most exciting were all the exotic plants of the new world suddenly available for observation, classification, and ultimately clarification. Geology and mineralology were beginning to face the problems of fossils. Every man who amounted to anything in the Renaissance had a curio cabinet with rocks, minerals, shells, fossils, and what not. Some of these were merely conversation pieces, junk for the idle curious, but many were studied systematically. Everyone was athirst for knowledge. Primitive notions of the vast antiquity of the earth were beginning to confront the rigid dogmas of sacred writings, interpreted literally. Science was born, and the amateurs of the Renaissance served as its numerous midwives.

The fifth wing should be of particular interest to physicians. It deals with anatomy and medicine. The impact of Vesalius upon his time; the peculiar combination of quack and wise man exemplified in Paracelsus, with his tentative approaches to experimental work, and strange people like Servetus, mystic and investigator, are described faithfully and with joy of humanism. The story of Fernel comes in for much interesting comment. The importation or outbreak of new diseases, such as syphilis; the recognition of scurvy as a hazard of the long and uncertain voyages on the ocean sea; the pervasive survival of witchcraft—all these things are woven into the story with great delight. Finally, Sarton's favorite, Leonardo da Vinci, is depicted an exemplar of the mating of art and science at a supreme pitch of accomplishment. He was a man of prodigious curiosity and enormous dexterity, whose lack of formal education may have prevented him from caring whether or not his contributions were recognized. Thus he made meager contributions to the art and science of his period and became famous by historical afterthought. The generally accepted estimate of this great man, deriving from a rather casual guess of Freud's, is restored to balance.

This book is a fitting monument to George Sarton and a tribute to the fruitful kind of scholarship which should make it clear to even the most unpretentious physician how true it is that history of science is science.

WILLIAM B. BEAN, M.D.

Research and Education in Rheumatic Diseases: Transactions of the Second National Conference. By Joseph J. Bunim, M.D. Gratis. Pp. 156. Arthritis and Rheumatism Foundation in Cooperation with National Institute of Arthritis and Metabolic Diseases, New York, 1958.

No physician is unaware of the needs of his arthritic patient, but a good number may not realize the ferment that has been generated in placing these needs on a stronger

scientific basis. Indeed, the groundwork in the related basic sciences covers an unusually broad area. Workers in one area benefit from contact with those engaged in other aspects of the problem; the physician is indebted to them all for contributions that underlie his management of his patients. This desire for mutual exchange led to these conferences in 1957 which have now been published. At that time, leading investigators and educators met to report progress made in rheumatic diseases, this conference following upon the success of the first one in 1953.

In this slim volume, a major portion is devoted to presentations of recent advances and promising leads by experts in such fields as enzyme chemistry, connective tissue metabolism, structure of collagen, experimental and human pathology, immunochemistry, anti-inflammatory agents, epidemiology, biometrics, and clinical investigation. Each is concisely stated. None offers detailed information, but these thumbnail sketches of individual problems provide as authoritative a summary of current rheumatic research as is available.

Coupled with this expanded research effort has been an increased number of training programs at the Medical School and postgraduate levels. Mainly through funds of the United States Public Health Service, such programs, which in many places are the backbone of the teaching program, are now in operation in thirty-one medical schools. Although more clinics, more hours of teaching, and more special courses have been provided, this knowledge has not generally permeated the ranks of the medical profession. The speakers recognize this and present various techniques they have found useful at their institutions to stimulate the interest of their students and colleagues.

All who are active in the rheumatic diseases and medical education will find this book valuable. Because of its compactness and concentration on the highlights it should be offered to others, including students, who may be interested in this field. It will afford them an elevation from which to survey an expanding frontier of medicine.

FRANK R. SCHMID, M.D.

Diagnostic Laboratory Hematology. Second revised edition. By Goerge E. Cartwright, M.D. Price, $6.75. Pp. 250, with 33 figures and 60 tables. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

The revised edition of this book has been expanded considerably to include a large number of important diagnostic tests, some of which had only recently been used in research but now have been adapted for use in the clinical laboratory. The author has presented in concise form the majority of procedures ordinarily used for diagnosis of hematological disorders. The tests include those used in office practice for examination of blood, enumeration of the formed elements of blood, techniques of bone marrow study, special stains of blood preparations, and tests concerned with hemorrhagic disorders, hemolytic disease, and the "L. E." phenomenon. Tests of blood, stool, and urine pigments related to hemoglobin are outlined, as well as a large number of miscellaneous examinations.

The author has tried to select a simple method for a given test which is based on simplicity, reliability, and accuracy and is one requiring inexpensive apparatus. Whether the test is concerned with the enumeration of erythrocytes, the determination of abnormal hemoglobin by paper electrophoresis, or the estimation of the prothrombin consumption, the precise details of the test are clearly outlined, leaving no steps to the imagination. At the end of each section instructions are given for the preparation of reagents. Sources for equipment and reagents are given when special standardization is required. References are given for those interested in original source material. The figures, charts, photographs, and diagrams are pertinent, clear, and well produced.

Throughout this book there is careful attention to the serious problem of errors in laboratory techniques and errors of method. The physician, student, or laboratory worker who reads this book will be reminded again that the laboratory value is not absolute and is not necessarily the final arbitrator in the clinical problem.

The use of these tests requires understanding of hematological disorders and general clinical medicine, and thus a minimal but helpful amount of explanatory material has been added to various sections. A brief paragraph of interpretation is included at the end of most of the sections. This is particularly helpful for tests with special significance or for understanding of newer methods of study.

Following the procedures outlined in this book would help any laboratory in reducing errors, improving services, and standardizing the performance of hematological tests. This

is an authoritative, well written, and useful book. It is recommended for the physician, medical student, laboratory worker, or technician who is concerned with hematology.

HENRY E. HAMILTON, M.D.

Ciba Foundation Colloquia on Endocrinology: Volume XII. Hormone Production in Endocrine Tumours. Edited by G. E. W. Wolstenholme, O.D.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. Price, $9. Pp. 351, with illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This twelveth edition of the Ciba Foundation Colloquia in Endocrinology is fairly typical in format of preceding volumes in this same series. A group of papers illuminating a basic aspect of development and study in endocrinology is presented, each by a man representing a specific discipline or study group related to the subject under discussion. Each of the papers, in turn, then is discussed by other members of the conference, all well known in the endocrine and biochemical fields.

There is extensive basic consideration of the anatomical, physiological, and biochemical characteristics of tumors of each of the endocrine glands, including the pituitary, both in the naturally occurring tumors in humans and in the experimentally induced tumors of these various types in animals. In the discussions on the experimental tumorigenesis in animals, it was pointed out by Dr. Gregory Pincus that there appear to be "remarkable repercussions of the effect of castration and irradiation leading to endocrine imbalance in the experimental animals, and the administration of hormone or the administration of goitrogen." He further suggests that there is a wide field for study existing in the interrelationship between one glandular system and another.

There is, of course, extensive experimental animal work reported in this volume, but perhaps of more immediate interest to clinicians who might be interested in this book is the large number of papers concerning various characteristics of these endocrine tumors in human beings. A particularly interesting paper by Dr. J. R. Tata, of the National Institute for Medical Research of London, describes the presence of an abnormal iodinated serum protein, which he designates as Compound X, which is found only in patients with functioning thyroid carcinoma and in approximately fifty per cent of these patients. The possible usefulness of this finding as a diagnostic test in thyroid cancer is pointed out in the discussions. There are other excellent papers on human tumor studies, including a discussion of biosynthesis of steroids in hyperactive and tumor-bearing human glands, by Dr. Ralph I. Dorfman. There are three papers concerned with hyperplasia and tumors of the human adrenal gland. One of these papers is from the Glasgow Royal Infirmary group; another, from the Sloan-Kettering Institute, and another, from the Yale University group. Other human tumors which are discussed are cystic ovaries, malignant testis tumors, islet-cell tumors (in reference to serum insulin determinations), and chromaffin-cell tumors.

All in all, this volume maintains the Ciba Foundation's high quality and high standard of excellence in gathering together men in related fields who might not otherwise have as adequate an opportunity to discuss and expand problems familiar to each of them. One important aspect of this book that has not been found in the other volumes is the inclusion of a cumulative index to all of the Ciba Foundation Colloquia on Endocrinology, from, Volumes I through XII. It makes this edition particularly valuable as an extensive endocrine bibliography source.

ROGER W. FRISKEY, M.D

Soldier in White: The Life of General George Miller Sternberg. By John M. Gibson. Price, $6.75. Pp. 277. The Duke University Press, Durham, N. C., 1958.

The average layman or physician might wonder why another biography of George M. Sternberg is needed, particularly since his wife Martha wrote such an excellent one forty years ago. There is much to be said for having a more critical biographer than a loyal, devoted, and capable wife. In "Soldier in White," John M. Gibson has provided us with a sound, well-documented, and eminently readable story of a physician who began his medical experience on the battlefield at Bull Run and was captured by the Confederates after the Federal picnic turned into a Confederate field day. Gibson has the wounded going by train to Charlotte, rather than Charlottesville, an error made in the earlier biography and perhaps excusable in a North Carolinian. Sternberg escaped and made his way back to Washington, where he was to become Surgeon-General of the United States Army and a very distinguished bacteriologist, teacher, and scientist.

Fortunately Sternberg was on the fighting lines and was spared much of the high-echelon confusion which dominated medical as well as military matters in the Civil War. Such confusion seems inevitable in military medicine in a democracy where each war is started amid chaos, little improved with belated plans suitable for the previous war. But he saw military medicine from the top to bottom. Experience fighting Indians and living the lonely life of an army surgeon during the great western expansion of the country did not prevent him from buying a precious microscope with his own money and teaching himself the necessary details of not only the preparation of slides and the new science of bacteriology but of microphotography, in which he became very expert. Some of his photomicographs are still showpieces. He also mastered foreign languages, which helped him at later international meetings, and invented an anemometer, only to find out that somebody else independently had patented the same device to measure wind velocity. He was more successful in his invention and patenting of a thermostat, making an automatic device in a mercury thermometer to make or break electric contact at a fixed temperature. This still serves as the basic model for most thermostats we now use.

Sternberg became a first-rate scientist. As a result of his energetic foresight he played an important role in establishing the Army Medical School, which has continued to serve a very important function in peace as well as during times of war. Sternberg himself had had to be his own teacher and guide in bacteriology. He was the father of medical research in the Armed Forces. Policies and practices he set in motion still play an important role in the health of soldiers and reached new heights in World War II, where the major medical research endeavor of the whole country was channeled albeit belatedly into applied and basic investigation of public health and military medicine.

It is very difficult to tell precisely what influence Sternberg had in the details of the brilliantly executed studies by Walter Reed and his colleagues in their dramatic unraveling of the mode of transmission of yellow fever. The two were close friends, sharing mutual respect and admiration. It is probable that many points not written into official documents were discussed by them. In any event, Sternberg provided the philosophic background against which research could exist and even flourish in an army which had thought of its medical responsibilities mostly in the most practical terms of applied medicine, amputating limbs, and patching the wounded. He was fortunate in seeing the results culminate in the control of yellow fever, with the development of the lands within the tropics which would never have been possible so long as yellow fever remained an epidemic scourge and malaria remained a chronic burden of woe. Sternberg's close practical experience in several epidemics of yellow fever which used to lash the coastal and inland ports of the country regularly during the nineteenth century lead him to interesting speculations about contagion, transmissibility, and various other epidemiological aspects of yellow fever which he helped in solving and bringing under control.

Contributions of American military medical men have had an important influence in medicine in the country out of all proportion to the numbers involved. The first great medical discovery made in this country came from the brilliant studies of William Beaumont, a series of admirable researches which led to an understanding of how the stomach functions in digestion. Sternberg, independently of Pasteur and others, discovered the pneumococcus, brought microscopy and photography together on a high level of science and artistry, and has his name perpetuated in an eponym attached to a peculiar type of cell found in Hodgkin's disease, but most of all should be remembered as the founder of the Army Medical School and the father of American scientific medicine in a military environment. While these may not be as great achievements as the monumental development by Billings, of the Surgeon-General's Library, now the National Medical Library; the historical and bibliographical achievements of Fielding Garrison during a life of only partial adjustment to military medicine; the building of the Army Medical Museum and its derivative Army Institute of Pathology, or the production of that massive repository of medical horrors to be found in the "Medical-Surgical History of the War of the Rebellion," 1870-1883, Sternberg set a standard of excellence in medical investigation and teaching which has had an abiding influence in the history of the country and on the history of medicine. These things he did while remaining a charming person, a devoted husband, a scholar, and a gentlemen of power, grace, and high ideals.

Gibson's biography sheds little new light on this distinguished man but tells his story in a straightforward and pleasant manner. For Civil War experts, there is very little more than the skirmish and capture at Manassas. But this biography does illuminate some of the prob-

lems of military medicine, and tells how science has contributed to the health of our army and our people and to what a large degree this was the achievement of Sternberg.

WILLIAM B. BEAN, M.D.

Advances in Electrocardiography. By Charles E. Kossmann, B.S., M.D., Med.Sc.D., F.A.C.P. Price, $9.75. Pp. 280, with 131 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

In this monograph, Dr. Kossmann and five of his co-workers present a review of advances in electrocardiography during the past decade, including previous and recent contributions of their own. Its background is a series of postgraduate courses in fundamentals of electrocardiography, and its aim is to narrow some of the gaps between progress made in various electrophysiologic laboratories and the needs of clinical electrocardiography.

The subject is presented under four principal categories. The first, dealing with present knowledge of the source of electrical potential, consists of chapters on the transmembrane potential, its ionic basis, and its experimental modifications, including electrical alternans and its relation to myocardial mechanics. Five subsequent chapters are devoted to the conducting medium, the dipole theory, the movement of the theoretical heart center, and the bearing of all these factors on the validity of various lead systems used in experimental and empirical electrocardiography and vectorcardiography. The spread of ventricular excitation and recovery under normal and abnormal conditions is considered in five chapters and includes a lucid discussion of the effects of electric images resulting from contiguity of media of different specific electrical resistances, which can account for some puzzling aspects of injury phenomena as well as "silent" areas of the subendocardium. Further, here included are discussions of the U-wave, of the place of the electrocardiogram in the diagnosis of hypertrophy, of principles of alterations attributable to congenital heart disease, and—in the longest chapter of the book—a summary and evaluation of systematic studies on mechanisms in intraventricular block. Disorders of cardiac rhythms are considered in a selective fashion from the standpoint of the various parameters of cardiac excitability, of their responses to some antiarrhythmic drugs, and of the manifestations of A-V nodal activity in experimental and clinical electrocardiograms.

Although the editor's coordinating influence is evident in cross references as well as in footnotes, some overlap in the presentation, and some discrepancies in viewpoints of the various authors seem unavoidable. For instance, in Chapter 13, the conventional classification of intraventricular block is adhered to, despite the introduction of a new classification in Chapter 10. With regard to the latter, the new terminology seems somewhat unclear in the author's own mind, considering the following formulation on page 133: "It is believed that both low-grade incomplete bundle branch block as well as minor degrees of high grade incomplete bundle branch block do not necessarily represent true blocks in bundle branch conduction."

Only a few items of the book are open to serious criticism. In Figure 1 of Chapter 16 (page 258), the assumption of "varying conduction to atria and ventricles" is incompatible with the preceding statement that the rates of the two chambers are "identical," and it is not supported by the type of variations of PQRS relationships encountered. Figures 3 and 4 of the same chapter represent, in my opinion, examples of a nodal (or lower atrial) ectopic tachycardia rather than repetitive reciprocal beating. The latter appears unlikely in view of the normal duration of the P-R intervals of the reproduced sinus beats. The statement on page 257 that concealed conduction in A-V dissociation refers to A-V nodal impulses is incorrect and reflects some misunderstanding of the original concept.

These critical remarks are not meant to detract from the excellence of the entire presentation. The authors are to be congratulated on their skill in selecting for discussion the most urgent problems of theoretical and practical electrocardiography; on their clarity in outlining established facts with the help of well-chosen references, illustrations, and diagrams, and on their ability to point out avenues for further possible advances in the field. This book is a unique contribution, outstanding among the numerous recent publications on the subject and a source of ample and stimulating information.

ALFRED PICK, M.D.

Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome. Edited by Jack Metcoff, M.D. Price, not given. Pp. 248, with 81 illustrations. The National Nephrosis Foundation, Inc., 143 E. 35th St., New York, 1958.

Three major problems related to nephrosis are discussed informally by active investigators. The first subject taken up is that of experimental nephritis produced by antigens and antibodies, mostly in the rat. The next subject discussed extensively is lipoprotein metabolism, and the third is electrolyte metabolism. Considerable data are presented by the participants in these sessions of the conference, but practically all the papers are in the nature of progress reports. As might be expected, agreement on many important points was not achieved. Perhaps this is best illustrated by the closing remark of the chairman of the first session, on antigens, antibodies, and renal lesions. He stated that he would "have another martini with Dr. Pfeiffer to talk things over." There is considerable discussion in this conference of interest to the investigator, and the reader certainly gets a good idea of the current thought and directions of experimental nephritis, lipoprotein, and electrolyte metabolism.

In another section, six investigators comment very briefly on work in progress in their own laboratories, and, finally, the conference discusses evaluation of steroid therapy in nephrosis. No one seemed at all satisfied with the methods of evaluation, but, nevertheless, there was little question that steroid therapy is effective to some degree.

DAVID EARLE, M.D.

Differentialdiagnose innerer Krankheiten: Eine kurzgefasste Darstellung für Arzte und Studierende. Fifth edition. By Prof. Dr. Robert Hegglin. Price, $18.95 (DM 79.50). Pp. 749, with 459 (some in color) illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, 1957.

This is the fifth edition of the widely used differential diagnosis of internal medicine in German language by the well-known Swiss clinician. In this book, the analysis of the leading symptoms is used in the discussion of diagnostic problems.

After an introduction of general aspects, the different symptoms are discussed is successive order. Etiologic classification of diseases is applied wherever possible and where etiology is known. However, the author's remark is well taken that differential diagnosis cannot be classified purely by pathologic physiological aspects, since this is not known in many instances.

Excellent illustrations help to understand the text and guide the reader in visualization of the described problems. The book is comprehensive and describes also rarities such as carcinoid of the digestive tract leading to endocardial fibroelastosis and right heart failure. However, even in a book of outstanding completeness such as this one, one may find that some symptoms are absent in the index. For instance, the symptom of vertigo cannot be found.

The book is an excellent reference and "gold mine" of knowledge. Its original approach is stimulating. It can be highly recommended for students, practicing physicians, and internists with command of the German language. The printing and illustrations are of the usual excellence of the publishing house.

PAUL KEZDI, M.D.

The Medical World of the Eighteenth Century. By Lester S. King, M.D. Price, $5.75. Pp. 346, The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1958.

Dr. King points out that there is no logic in using a century as a dividing marker in historical studies. Such devices are convenient, since they put the past into manageable packets. Perhaps historians of the distant future will see in the eighteenth century the clear signs of the emergence of what we call modern-day medicine. The problems are very much the same. They are discussed in historical perspective, mainly through the medium of biographical sketches of prominent physicians of the period, by an analysis of their writings, textbooks, practices, ideas, and ideals. The story begins with the age old feud between apothecaries and physicians. In the days before asepsis and anesthesia, surgery was heroic, bloody, and often fatal. The vast preponderance of the practice of medicine lay in the administration of the most extravagant array of unusual concoctions, provided by the apothecary, but in many cases of his own prescribing after the manner of some today. Dr. King's material is presented fairly, pointing out that by no means were physicians always free from error in their dealings with the less well-trained but no less greedy apothecaries. The feuds, legal battles, the great hurlyburly of medicine in England, particularly in London, are portrayed vividly. Since orthodox physicians were not numerous enough to go around, there was a need for apothecaries.

This need was filled often by those who had had no training even in the primitive pharmacology of the day. Thus quacks and empirics, boasting of fabulous cures, advertised by very effective word of mouth, would move in, announce their magical cures, obtain some enthusiastic supporters, and fleece the public. Calamitous failures made them hurry away to escape to their next scene of activity.

Much space is devoted to Hermann Boerhaave, a teacher whose influence pervaded all Europe and spread to America by way of Scotland. It was his parents' intent that he be a minister, and he was educated to this end. He became fascinated with science and mathematics, took further degrees, and ultimately studied medicine. Because of accusations of atheism, he was forced to practice medicine rather than the ministry. In his prime, though he commanded a very small clinic, he became the great doctor and teacher of medicine of his day. His bedside teaching, his lectures, and his publications carried tremendous weight. He owes a great debt to his numerous and brilliant pupils. Of these, van Swieten, who published eighteen volumes of commentaries on Boerhaave's aphorisms, deserves most credit for establishing his master's historic reputation.

The important corrective effect which Hahnemann and the school of homeopathy gave orthodox medical therapy of the eighteenth century was chiefly a demonstration that much therapy had been toxic nonsense based on authoritative ignorance. This bitter, powerful, and often tragic man inadvertently did a service to orthodox medicine by creating sceptics where before most had been gullible believers.

Conceptions of disease began to change with the rise of pathology, the widespread examination of the dead, and the sudden realization that facts and information could be used to establish classifications of disease. Nosology, which often went too far, reached its acme in the extravagant minutiae of Sauvages, who had 44 orders and 315 genera of disease entities, which, divided into species, enabled him to list 2,400 different diseases in all. The limitations of nosology and the always tentative state of any system of classification were hardly recognized. It was believed that disease entities existed in nature rather than as convenient symbols in the mind of a physician to help him in his practical dealings with the situation which prevails when a particular person receives particular stimuli which upset the functions of health.

Medical ethics was beginning to emerge, not, as many people believed, from religious idealism but as a practical guide for professional etiquette in the dealing of physicians with each other and with patients. From such recent roots have come our present views, which actually go back to the days before Hippocrates, when there was some form of code. The practice of medicine, its continuous and better realized dependence on observations and experiments, was beginning to show what might be done when the natural history of disease was observed shrewdly. Then the nature of evidence and the growing scientific attitude began to create new opportunities and disclose how a better understanding of health and disease make possible improvements in therapy even if those improvements consist of nothing more than letting well enough alone. The curious human addiction to systems, doctrine, and dogma, in which all-encompassing mental constructs take on the cast of reality and determine the direction of practice, foibles still prevailing today, is illustrated in the therapeutic orgies of Brown and the blood baths of the heroic but arrogant, pig-headed, and utterly mislead Rush. These examples combine elements of tragedy, which almost hide the comical features of these all too human beings.

This book is full of interest. It is more a collection of essays and biographical sketches than a cohesive history of the period, but such a history would take a lifetime of study and many volumes. King has done a good job in putting before us many of the important men and movements of medicine in the eighteenth century. They are worthies in the slow march of change.

WILLIAM B. BEAN, M.D.

The Essence of Surgery. By C. Stuart Welch, M.S., M.D., Ph.D., and Samuel R. Powers Jr., A.B., M.D., M.Sc.D. Price, not given. Pp. 320, with 50 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

This book deals with the principles basic to surgery. It is a book of generalities, briefly presenting specific entities to illustrate these principles only.

A very interesting sketch of surgical history introduces the book. Then follows the definition of surgery as the management of acute injury and a discussion of its three subdivisions, which include loss of body tissue (wounds and wound healing), loss of body fluids, and infection.

Time-honored principles of pre- and postoperative care are presented, and then the rudiments of operative technique are discussed, including asepsis, hemostasis, and soft tissue dissection. A warning against overspecialization is sounded. The book next deals with the major categories of operative procedures, defined by the authors as extirpative, reconstructive, and physiologic surgery and the treatment of wounds. A brief chapter on anesthesiology, contributed by Gerard Converse, M.D., concludes the book.

The format of the book is pleasing; the index adequate, and the illustrations are appropriate and simple. The bibliography has been selected with care and economy of number but is not related numerically to the text or chapters. As in all first editions, the book contains a handful of relatively unimportant typographical errors. The text is concise, lucid, and interesting.

The authors are to be congratulated for the high quality of writing and the carefully chosen principles which they have stressed. The book will be particularly useful to medical students being introduced to the subject of surgery, but its philosophies are equally valid and interesting at all levels of surgical disciplines.

ROBERT T. SOPER, M.D.

Chlorothiazide and Other Diuretic Agents. John V. Taggart, Consulting Editor. Price, not given. Pp. 155, with 96 illustrations. New York Academy of Sciences, 2 E. 63d St., New York 21, 1958.

This series of papers was presented at a conference on diuretic agents held in New York on Nov. 8, 1957. It was sponsored by the New York Academy of Sciences and the manufacturer of chlorothiazide.

The papers and the discussions of them present an interesting group of observations about diuretic agents in general and about chlorothiazide in particular. The prime purpose of the conference appeared to be a timely and a wise attempt on the part of both sponsors to gather a large group of basic and clinical scientists to discuss an important new drug before its general release. This purpose was achieved. Many problems of the administration of chlorothiazide were dealt with in detail, and important areas needing study were outlined. A complete and accurate picture of the effect of chlorothiazide when used in edematous and hypertensive patients over a relatively short-term period was given. More important, practically all of the advantages and problems of this drug were presented to those gathered at the meeting and through the medium of this series of papers to all practicing physicians at a time when the drug was first becoming generally available.

To a certain extent a by-product of the conference, nevertheless the discussions of the chemistry and mode of action of diuretic agents were interesting and important contributions. These papers, plus the chlorothiazide ones and two on electrolyte metabolism, make up the volume.

I found this collection of papers a very useful publication. Compressed in it are most of the facts known about chlorothiazide. Because these matters were presented before an audience of people interested in the drug, areas of agreement and disagreement are clearly highlighted in the discussions.

Although many other drugs have been introduced in this fashion, I think it should be mentioned that this is a practical, timely, and honest method of calling attention to a significant new product. Such endeavors as this conference seem a much better way for drug companies to spend their money to promote a drug than the bright-colored, eye-catching pieces of "literature" which now fill our wastebaskets. There is no doubt that biochemists, physiologists, and physicians interested in diuretic agents will find this volume useful and will salute its publication.

WALTER M. KIRKENDALL, M.D.

News and Comment

ANNOUNCEMENTS

Series on the Growth of Medicine.—Northwestern University Medical School will present another series of papers on the Growth of Medicine at the Ward Building, 303 Chicago Ave., Chicago. The subjects and the dates are as follows:

M. David Allweiss, M.D. Associate in Medicine, Northwestern University Medical School Associate Attending Physician, Michael Reese Hospital	Hippocrates	Jan. 6
Samuel Zakon, A.A., M.D. Professor of Dermatology, Northwestern University Medical School	Maimonides	Jan. 13
Frederick Stenn, M.S., M.D. Assistant Professor of Medicine, Northwestern University Medical School	Osler	Jan. 20
Ralph Reis, M.D. Professor of Obstetrics and Gynecology, Northwestern University Medical School Attending Obstetrician and Gynecologist, Passavant Memorial Hospital	Semmelweiss	Jan. 27
Arthur Stillians, M.D. Professor of Dermatology, Emeritus, Northwestern University Medical School	von Hebra	Feb. 3
Guy Youmans, M.S., Ph.D., M.D. Professor and Chairman Department of Microbiology, Northwestern University Medical School	Pasteur	Feb. 10
Abram Cannon, M.D. Associate in Radiology, Northwestern University Medical School	Roentgen	Feb. 17
Michael Mason, M.A., Ph.D., M.D. Professor of Surgery, Northwestern University Medical School	Lister	Feb. 24
Barry J. Anson, M.A., Ph.D. Chairman and Robert Laughlin Rea Professor of Anatomy, Northwestern University Medical School	Pare	March 3
Jerome R. Head, M.A., M.D. Associate Professor of Surgery, Northwestern University Medical School	Laennec	March 10

International Congress of Gastroenterology.—The Sixth Meeting of the Association of the National European and Mediterranean Societies of Gastroenterology, organized by the Association of Dutch Gastroenterologists, will be held in Leiden, the Netherlands, from April 20 to 24, 1960.

The main themes of the conference will be (1) pathology of the small intestine and (2) hepatitis, cirrhosis hepatis, and their possible connection.

Panel discussions, lectures and film shows will be arranged in connection with these themes and related subjects. Scientific and technical-commercial exhibits will be also organized.

Original reports on these subjects or any other gastroenterological subject, either clinical or in the field of the basic sciences, are invited for submission and will be accepted for panel discussion or publication if approved by the Scientific Program Committee.

Titles for papers together with a summary of not more than 200 words should be sent not later than Aug. 1, 1959, to Dr. B. K. Boom, Congress Office, Department of Gastroenterology, University Hospital, Leiden, the Netherlands.

Official language: English.

Working languages: English, French, German, Spanish (with simultaneous translation).

Registration fee (including an official reception, a banquet and an excursion) for full member, U. S. $45; for accompanying family members, U. S. $20. After Nov. 1, 1959, the registration fee for full members will be U. S. $55. The fees quoted in U. S. dollars can be paid also in Dutch guilders or any other transferable currency.

For further information and registration apply to the Congress Office of the Sixth Meeting of the Association of the National European and Mediterranean Societies of Gastroenterology, Department of Gastroenterology, University Hospital, Leiden, the Netherlands, or the Secretary of the national societies of gastroenterologists.

Continuation Course in Internal Medicine.—The University of Minnesota announces a continuation course in Internal Medicine for Internists to be held at the Center for Continuation Study on the University Campus from March 16 to 18, 1959. Areas to be covered this year include diseases of the kidney and gastrointestinal tract, chemotherapy of cancer, and clinical uses of steroids.

Guest speakers will include Doctors Robert M. Kark, Professor of Medicine, University of Illinois College of Medicine, Chicago; Joseph B. Kirsner, Professor of Medicine, University of Chicago School of Medicine, Chicago; and Richard I. Smith, Rheumatologist, Philadelphia. Remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and the Mayo Foundation. The course will be presented under the direction of Dr. Wesley W. Spink, Professor, Department of Medicine.

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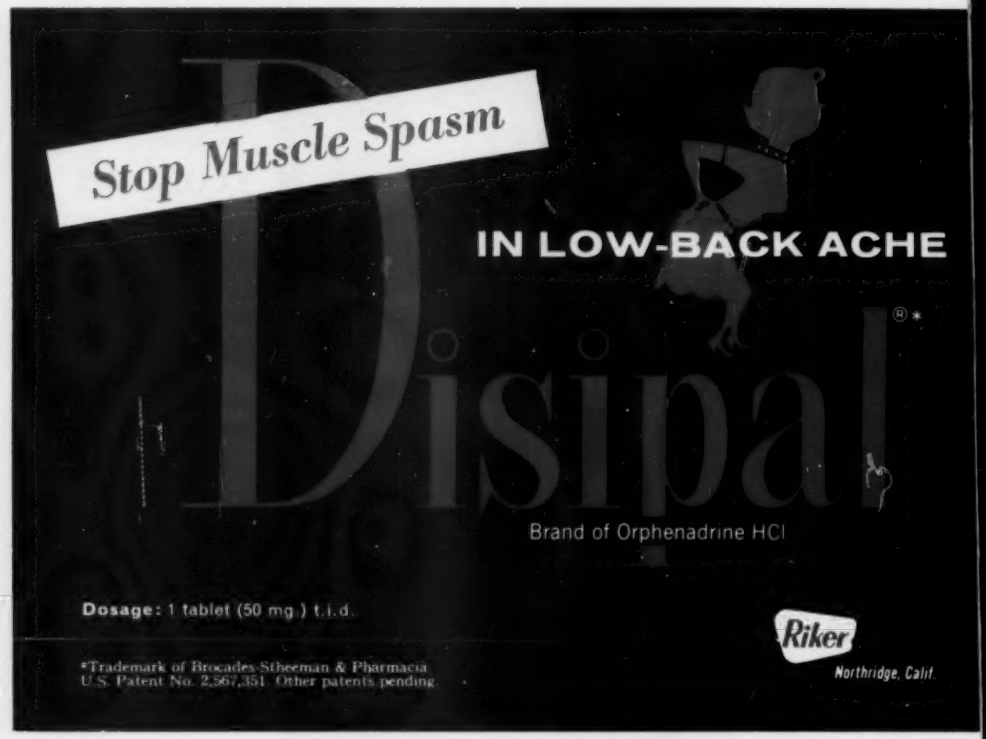

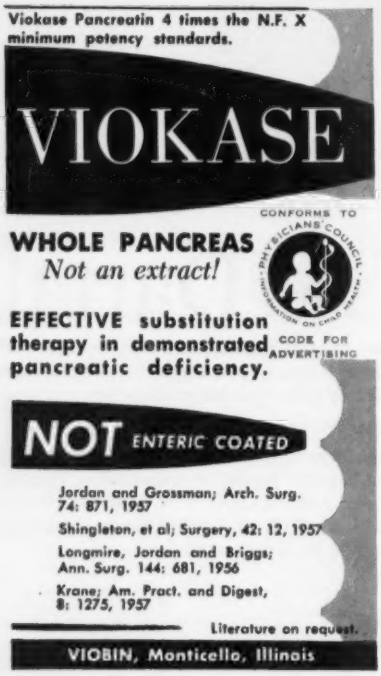
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Jordan and Grossman; Arch. Surg. 74: 871, 1957
Shingleton, et al; Surgery, 42: 12, 1957
Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956
Krane; Am. Pract. and Digest, 8: 1275, 1957
Literature on request.
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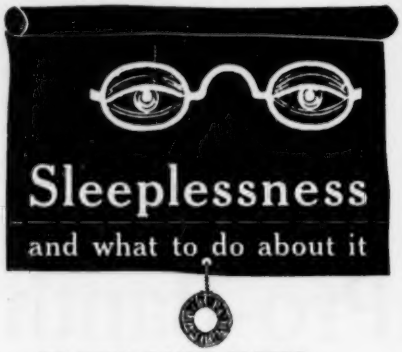

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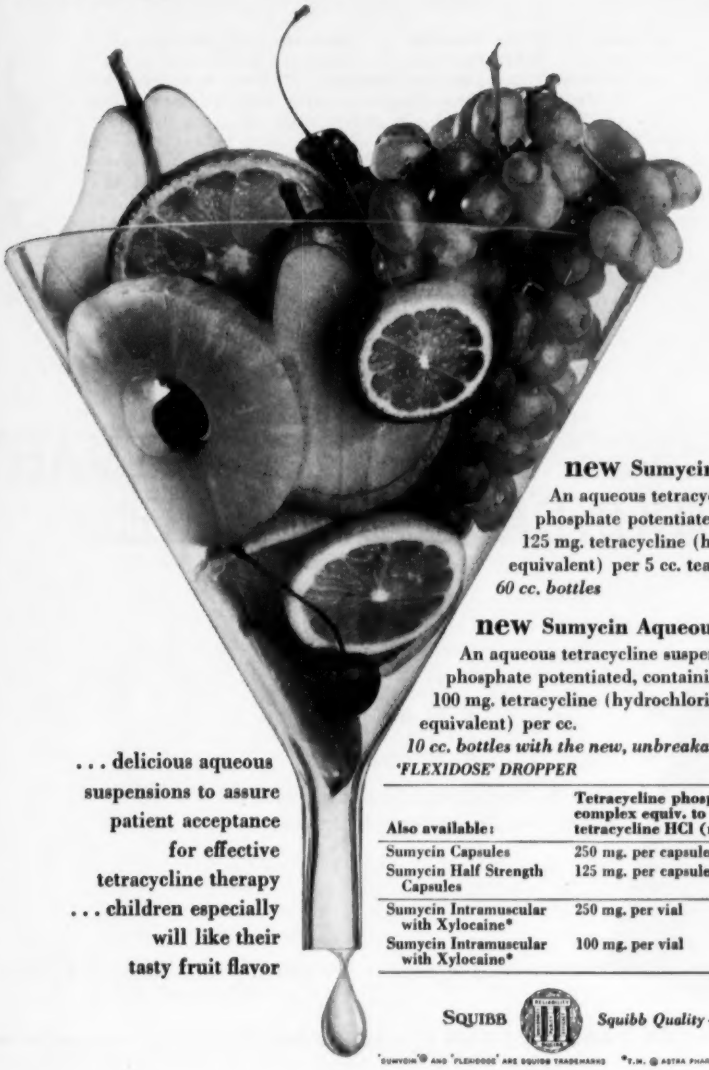

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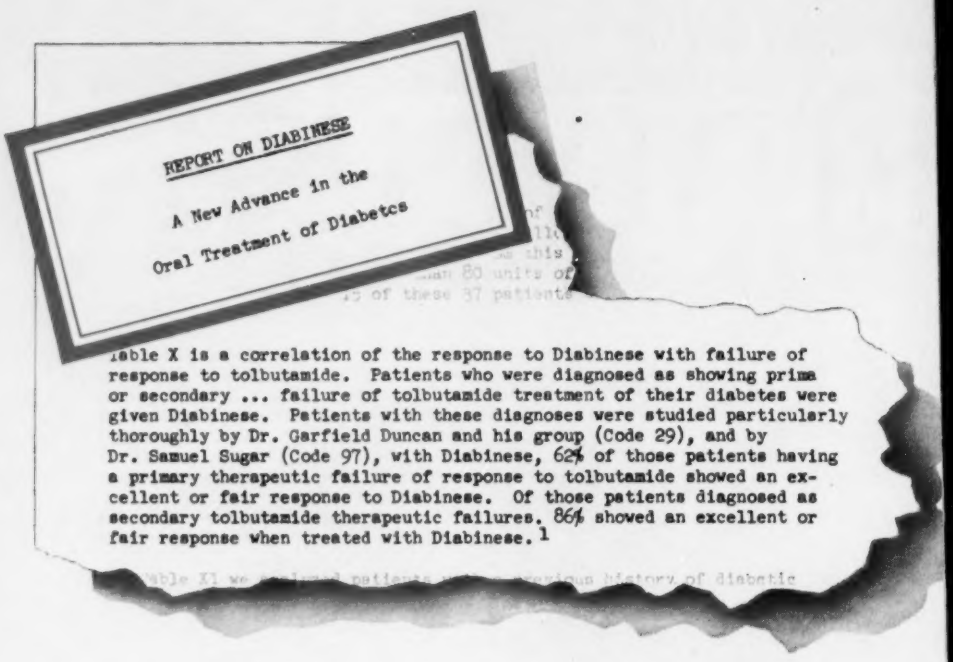
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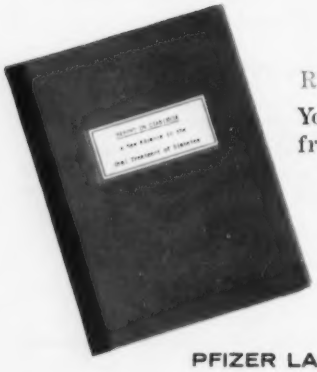

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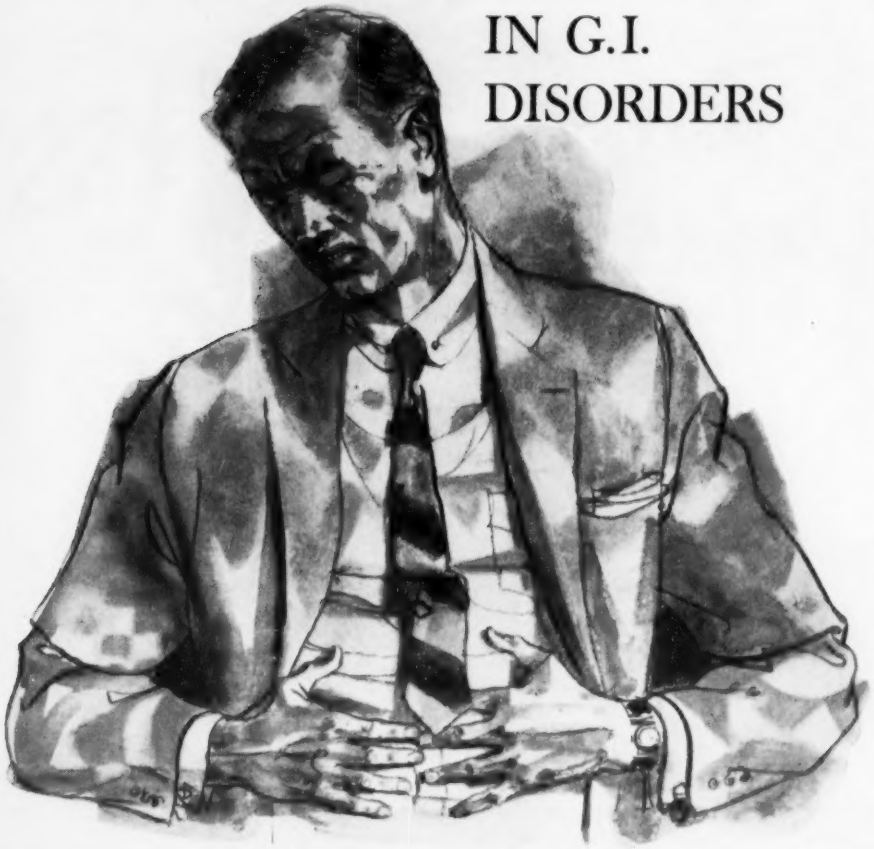

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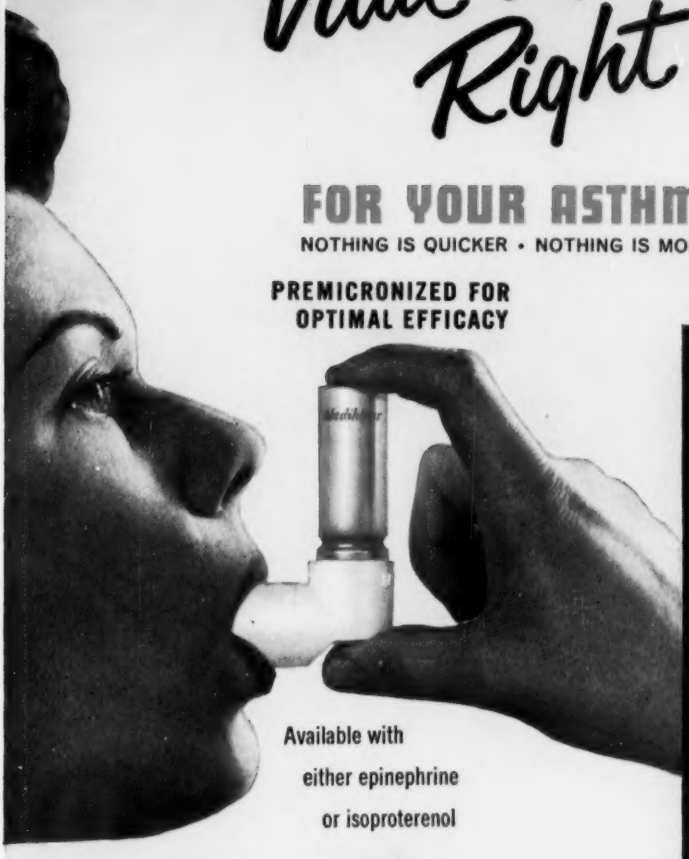

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